# Total Synthesis of (–)-Pyridovericin and Synthetic Studies towards Aetheramide B

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*The wind was flapping a temple flag, and two monks started an argument. One said the flag moved, the other said the wind moved.*

*The sixth patriarch said:" It is not the wind that moves, it is not the flag that moves; it is your mind that moves."*

*Mumonkan*, *Case 29*

# Table of Content

*Parts of this PhD thesis have been published similarly or identical in the following publications:*

**Chapter 2:**

Fabian Schmid, Henning J. Jessen, Maurizio Bernasconi, Andreas Pfaltz, Karl Gademann, **Catalytic Enantioselective Total Synthesis of (–)-Pyridovericin**, *Synthesis* **2014**, *46*, 864.

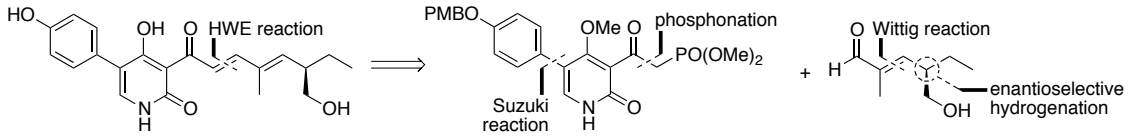
Patrick Burch, Fabian Schmid, Karl Gademann, **Neuritogenic Surfaces Using Natural Product Analogs**, *Adv. Healthc. Mat.* **2014**, *3*, 1415.

Fabian Schmid, Henning J. Jessen, Patrick Burch, Karl Gademann, **Truncated Militarinone Fragments Identified by Total Chemical Synthesis Induce Neurite Outgrowth**, *Med. Chem. Commun.* **2013**, *49*, 155.

Henning J. Jessen, Andreas Schumacher, Fabian Schmid, Andreas Pfaltz, K. Gademann, **Catalytic Enantioselective Total Synthesis of (+)-Torrubiellone C**, *Org. Lett.* **2011**, *13*, 4368.

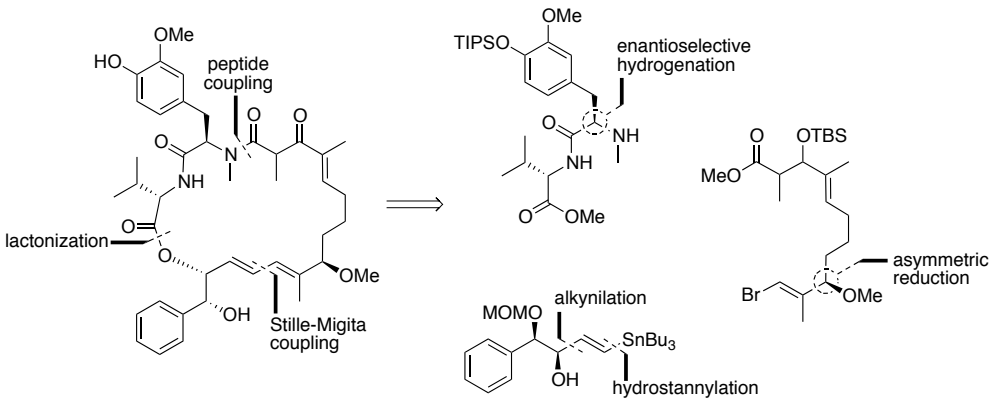
# Abstract

In this thesis, two projects involving the total synthesis of natural products are presented. The first chapter gives a general introduction to natural product total synthesis and its impact on human society.




**(–)-Pyridovericin**

The second chapter gives an overview on neurodegenerative diseases and introduces the neuritogenic pyridopolyene natural product (–)-pyridovericin. The enantioselective total synthesis of (–)-pyridovericin is presented. The key steps were an enantioselective, iridium-catalyzed hydrogenation of an enoate and an *E*-selective Horner-Wadsworth-Emmons reaction. The complex pyridopolyene structure was then truncated and the neuritogenic core structure identified. Truncated natural product analogs were synthesized and successfully implemented in a neuritogenic surface material.

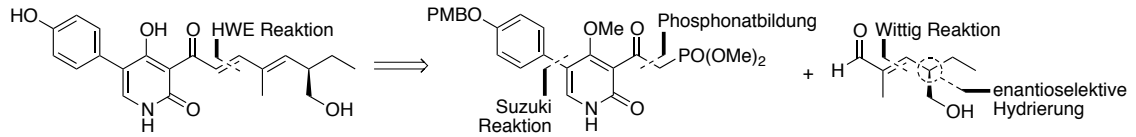



**Aetheramide B**

The third chapter reviews the current state of research on HIV and AIDS. Our efforts towards the total synthesis of the recently isolated HIV-inhibitory natural product aetheramide B are reported. Three advanced building blocks were synthesized enantioselectively in good yields. The key steps involved the enantioselective hydrogenation of an enamide to form an amino ester, the diastereoselective alkynylation of a homobenzylic aldehyde and the enantioselective reduction of a bromoenone. The building blocks were then successfully coupled to form the macrocyclic depsipeptide core structure. The macrocyclic core of aetheramide B was then synthesized in a macrolactonization reaction.

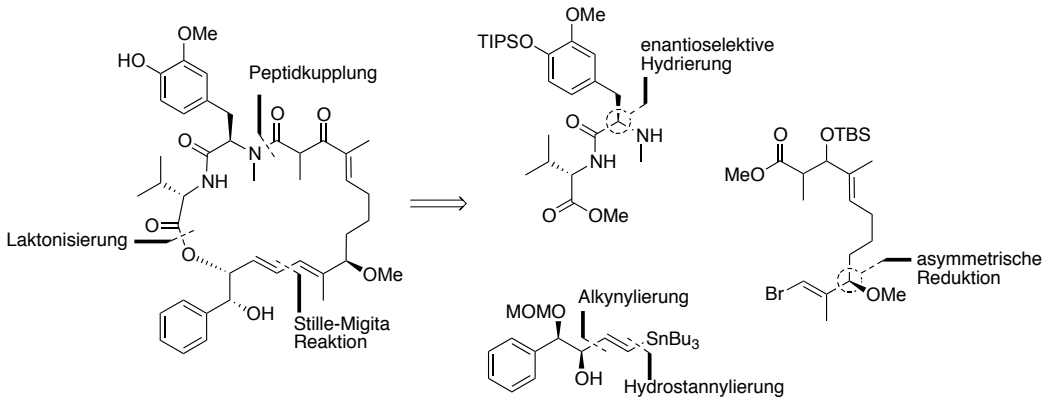
## Kurzbeschreibung

Diese Doktorarbeit umfasst zwei Projekte, die sich mit der Totalsynthese von Naturstoffen und deren Anwendungen befassen. Im ersten Kapitel wird an einigen historischen und modernen Beispielen die Bedeutung der Naturstoffsynthese illustriert.




**(–)-Pyridovericin**

Im zweiten Kapitel wird die enantioselektive Totalsynthese von (–)-Pyridovericin beschrieben. Die Schlüsselschritte umfassen eine enantioselektive, asymmetrische Hydrierung eines ungesättigten Esters und eine Horner-Wadsworth-Emmons Reaktion zur Verknüpfung der Hauptfragmente. Die neuritogene Grundstruktur wurde mithilfe von PC-12 Assays ermittelt, und das erhaltene Naturstoffanalogon wurde zur Herstellung einer biokompatiblen, neuritogenen Oberfläche verwendet.




**Aetheramid B**

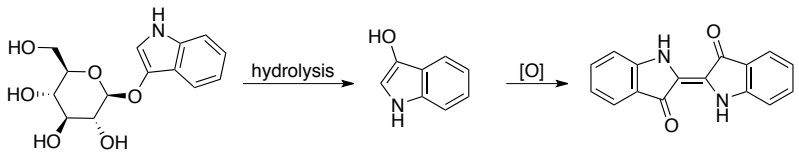
Eine Einleitung zum *Status Quo* der HIV-Pandemie und AIDS-Therapie bildet den Auftakt zu Kapitel drei. Die Fortschritte in der Totalsynthese des HIV-inhibierenden Depsipeptids Aetheramid B werden präsentiert. Drei Hauptfragmente wurden in guter Ausbeute und hoher Enantiomerenreinheit synthetisiert. Die Schlüsselschritte umfassten eine Rhodium-katalysierte, enantioselektive Hydrierung zur Herstellung des Dipeptid-fragments, eine diastereoselektive Alkynylierung zur Darstellung des Diol-fragments und eine enantioselektive Reduktion eines labilen Bromenons. Die Fragmente wurden erfolgreich zusammengefügt, und die markozyklische Grundstrunktur von Aetheramid B wurde in einer Macrolaktonisierungsreaktion synthetisiert.

# 1 Introduction

## 1.1 Natural Product Chemistry in Human History

Throughout history, biological matter (e.g. animals, plants, fungi, microorganisms) has been a great source of materials beneficial to human society. This general introduction aims to highlight a selection of historic applications and discoveries of natural products in several fields relevant to human society.

Indigo (**1.03**) is a blue dye used in textile dying obtained from the extracts of plants from the genus *Indigofera* (Scheme 1.1). Historically, indigo production has been performed in Asia (especially India) for centuries, and the first reports of the dye being used in Europe date back to the Greco-Roman era.[1] In general, dyes were highly scarce until the 19th century, and one of the economical driving forces of the colonization and exploitation of south and Southeast Asia has been the export of indigo.[2] In the pre-industrialization era, indigo was the only available blue dye and, even today, denim blue jeans derive their characteristic color from indigo.




indican (**1.01**) indoxyl (**1.02**) indigo (**1.03**)

**Scheme 1.1**: Formation of Indigo (**1.03**) from indican (**1.01**).

The *Indigofera* plants are rich in the water-soluble and colorless indol-substituted sugar, indican (**1.01**), which is extracted from the plant and hydrolyzed to give the colorless and water-soluble indoxyl (Scheme 1.1). When exposed to the oxygen present in air, indol **1.02** undergoes an oxidative dimerization to form the water-insoluble indigo (**1.03**).[3] Since 1897, an industrial chemical process developed by BASF has largely replaced the extraction route to indigo.

[1] E. Steingruber, Indigo and Indigo Colorants, *Ullmann's Encyclopedia of Industrial Chemistry*, **2004**, Wiley-VCH, Weinheim.
[2] D. H. Rembert, *Jr. Economic Botany,* **1979**, *33*, 128.
[3] M. Sequin-Frey, *J. Chem. Educ.* **1981**, *58,* 301.

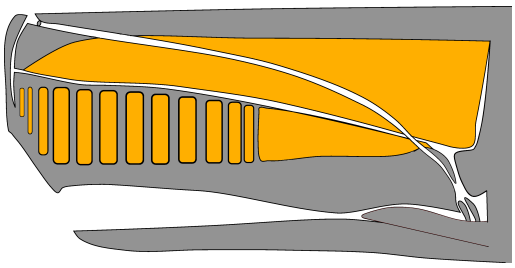
The initial syntheses reported by Adolf von Baeyer in 1882 proved to be too impractical for industrial scale, and a modified process based on the method by Heumann and Hegler is still applied today, producing about 17,000 tons per year.[4]

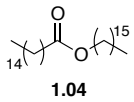
**Figure 1.1**: Stripping sperm whale of blubber (left) and extraction of spermaceti from the whale's head (right).[5]

Before the advent of the petrol industry and electrification, people relied on other sources of energy for the generation of light. The organic oils and waxes found in *Cetaceans* proved to be highly useful for this purpose, and especially *Physeter macrocephalus*, commonly known as sperm whale, suffered tremendously due to this fact. The main sought after component of the sperm whale was on one hand the blubber. This greasy adipose tissue under the skin of the whale was peeled off (Figure 1.1, left) and boiled to give the refined whale or tran oil, which was used to fuel lamps for example.[6] On the other hand, the product that distinguished the sperm whale from other *Cetaceans* is the spermaceti or sperm oil found in the whale's head (Figure 1.1, right and Figure 1.2). This colorless waxy substance (M.p. ~ 40°C) consists mainly of wax esters such as cetyl palmitate (**1.04**, Figure 1.2),[7] which gives a very bright light when manufactured into candles.

[4] A. von Baeyer, V. Drewsen, *Ber.* **1882**, *15,* 2856; H. Schmidt, *Chemie unseres Zeit,* **1997**, *3*, 121.
[5] W. M. Davis, Nimrod of the Sea; or, The American Whaleman,**1874**, public domain.
[6] W. F. Perrin, B. Würsig, J. G. M. Thewissen, *Encyclopedia of Marine Mammals*, **2002**, Oxford Academic press, 2nd edition, Oxford.
[7] M. R. Clarke, *Nature* **1970**, *228,* 873.

Even early standardization protocols for the definition of luminous intensity relied on the use of a pure spermaceti candle.[8] Nowadays, jojoba oil and synthetic cetyl palmitate (**1.04**) replace the products of whale origin in cosmetics, lubricants etc.






**1.04**

**Figure 1.2**: Cross section of sperm whale head (left) with spermaceti in gold and its main constituent cetyl palmitate (**1.04**, right).[9]

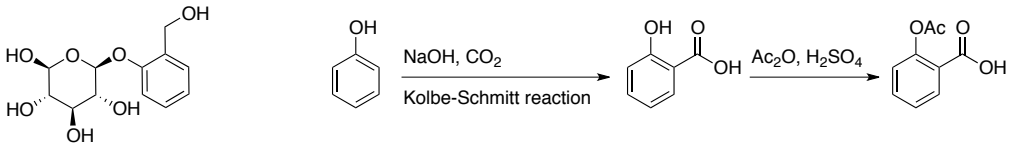
These two historic examples clearly illustrate some of the many merits of organic synthesis. Both the extraction of indigo and whaling of sperm whales have negative impact on the ecosystem. While the production of indigo largely proceeded under miserable conditions for the indigenous work force, also sperm whaling was a risky and strenuous undertaking for the crew and also nearly lead to the extinction of sperm whales. The processes were also economically unattractive, since the products usually had to be shipped over large distances. The synthetic preparation of indigo (**1.03**) and cetyl palmitate (**1.04**) allowed for production on-site and eliminated the drawbacks of the classical fabrication.

## 1.2 Natural Products in Medicinal Applications

One of the most distinguished uses of natural products has been their application in a medicinal context. The earliest documented case of plants applied as medicine date back to 60'000 BC, found in the grave of a Neanderthal in the Shanidar cave.[10] Several written documents detail the preparation of plant tinctures and extracts, such as clay tablets from Mesopotamia (2600 BC), the Chinese "*Wushi'er Bingfang*" (1100 BC) or the Ebers papyrus (2900 BC).[11] The Ebers papyrus lists extracts of willow barks with an analgesic and anti-inflammatory properties, and willow extracts have also been used in

[8] "Chartered Gas Light and Coke Company". *London Metropolitan Archives*. The National Archives. 1823–1894. pp. LMA/4438.
[9] http://commons.wikimedia.org/wiki/File:Cross_section_of_a_sperm_whale_head.png, CC0-1.0 universal public domain dedication license.
[10] A. Lerio-Gourhan, *Science,* **1975***, 190*, 562.
[11] G. M. Cragg, D. J. Newman, *Pure Appl. Chem.* **2005**, *77*, 7.

Europe since 4000 BC.[12] With the emergence of modern scientific methodology in the 19th century, the pharmacologically active constituents of the willow formulations were further investigated. Salicin (**1.05**) was isolated in 1828 by Joseph Buchner[13] and, by 1874, salicylic acid (**1.07**) was produced industrially *via* the Kolbe-Schmitt process (Scheme 1.2).[14]




**1.05** **1.06** **1.07** **1.08**

**Scheme 1.2**: Structure of salicin (**1.05**) and the synthesis of Aspirin (**1.08**).

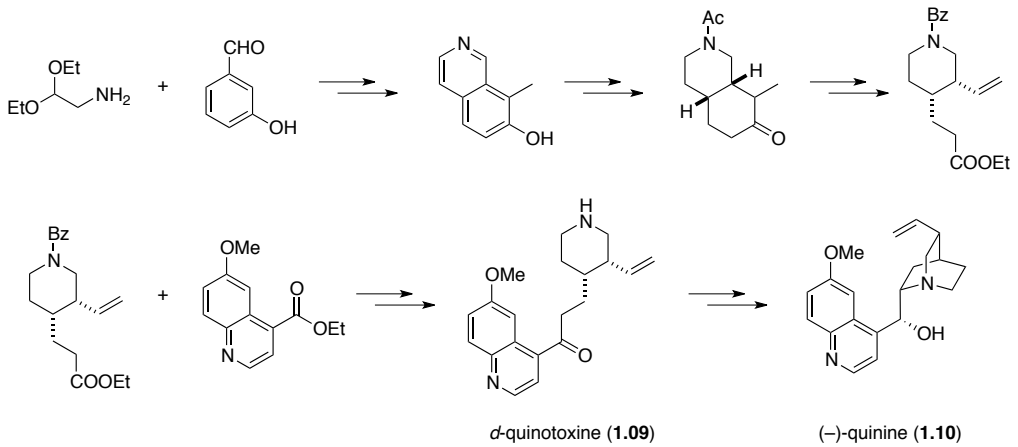
Although glycoside **1.05** possesses analgesic and anti-inflammatory properties, it was found that acetyl salicylic acid (**1.08**, trade name Aspirin) had less side effects, especially gastric irritation, and was patented in the U.S. in 1900 by Bayer.[15] In the production process, phenol (**1.06**) is oxidized to salicylic acid (**1.07**) in the presence of sodium hydroxide and carbon dioxide. Acid **1.07** is then acetylated with acetic anhydride in the presence of either catalytic amounts of sulfuric acid or pyridine to give aspirin (Scheme 1.2). Aspirin (**1.08**) also possesses further modes of action than glycoside **1.05**, and Bergström, Samuelsson and Vane, the investigators of the prostaglandin inhibiting properties of Aspirin, were awarded with the Nobel Prize in medicine and physiology in 1982.[16]

For centuries, the barks of *Cinchona* trees have been used by the indigenous Peruvian Quechua people as a muscle relaxant.[17] The bark was then brought to Europe in the 16th century by Jesuit priests for the treatment of malaria and called Jesuit's or Peruvian bark. It is argued that the discovery of the Peruvian bark fuelled the colonization of the

[12] K.-C. Bergmann, J. Ring, *History of Allergy* **2014**, Karger Medical and Scientific Publishers, Basel.
[13] O. Lafont, *Rev. Hist. Pharm.* **2007**, *55*, 209.
[14] H. Kolbe, E. Lautemann, *Liebigs Ann. Chem*. **1860**, *113*, 125; H. Kolbe, E. Lautemann, *Liebigs Ann. Chem*. **1860**, *115*, 157; .Patent US334290: *Manufacture of salicylic acid.* Published January12. **1886**, Inventor: R. Schmitt.
[15] W. Sneader, *BMJ*, **2001**, *321,* 7276.
[16] J. R. Vane, *Nat. New Biol.* **1971**, *231*, 232.
[17] R. Fiametta, *Quinine: malaria and the quest for a cure that changed the world* **2004**, NY: Perennial, New York.

sub-Saharan African continent and allowed for permanent establishment of settlements in the malaria-endemic regions.[18]

The antimalarial agent in *Cinchona* barks was first isolated in 1820 by Pelletier and Caventou and called quinine (**1.10**),[19] but it wasn't until 1908 when the correct structure of compound **1.10** was determined by Rabe (Scheme 1.3).[20] Until the 1940's, quinine (**1.10**) remained the treatment of choice for malaria. When the U.S. supply line of *Cinchona* bark from Javanese plantations run by the Dutch monopoly was cut during the German occupation of the Netherlands, it caused the death of thousands of U.S. soldiers stationed in the Pacific due to malaria infection. This devastation motivated investigations towards a synthetic route to quinine (**1.10**) and related *Cinchona* alkaloids, which culminated in the historic formal synthesis of (–)-quinine (**1.10**) from precursor **1.09** by Woodward and Doering in 1944 (Scheme 1.3).[21]




*d*-quinotoxine (**1.09**) (–)-quinine (**1.10**)

**Scheme 1.3**: Total synthesis of *d*-quinotoxine (**1.09**) and formal synthesis of (–)-quinine (**1.10**) by Woodward and Doering.

Since then, *Cinchona* alkaloids have found widespread application in asymmetric organic synthesis.[22] Despite the controversy surrounding the original report,[23] it served as a benchmark for other synthetic organic chemists, as did many of Woodward's

[18] J. Achan, A. O. Talisuna, A. Erhart, A. Yeka, J. K. Tibenderana, F. N. Baliraine, P. J. Rosenthal, U. D'Alessandro, *Malaria Journal* **2011**, *10*, 144.
[19] P. J. Pelletier, J. B. Caventou, *Annales de Chimie et de Physique* **1820**, *15*, 337.
[20] P. Rabe, *Ber.* **1908**, *41*, *62.*
[21] R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1945**, *66,* 849; R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1945**, *67,* 860.
[22] C. E. Song (Ed.), *Cinchona Alkaloids in Synthesis and Catalysis: Ligands, Immobilization and Organocatalysis*, **2009**, Wiley-VCH, Weinheim.
[23] A. C. Smith, R. M. Williams, *Angew. Chem. Int. Ed.* **2008**, *47*, 1736; J. I. Seeman, *Angew. Chem. Int. Ed.* **2007**, *46*, 1378.

works.[24] It further shifted the expectation of the amount molecular complexity able to be achieved by total synthesis, especially in a medicinal chemistry context.

## 1.3 Total Synthesis of Natural Products and Drug Development

In 1929, Scottish biologist Alexander Fleming observed the inhibition of bacterial growth in a *Staphylococcus* culture by a contaminant mold, which was identified to be the fungus *Penicillium notatum* (Figure 1.3).[25] The structure of the antibacterial compound was proposed in 1941 and confirmed in 1944 by X-ray crystallographic analysis of penicillin G.[26] The β-lactam core **1.12** was later also found to be present in cephalosporin type antibiotic natural products (**1.13**, Figure 1.4).[27] It was found that β-lactam antibiotics inhibit cell wall synthesis in the bacterium by binding to penicillin-binding transpeptidases.[28] Since the first commercial production of penicillin by fermentation during the Second World War, the emergence of penicillin resistant bacterial strains posed a severe health threat. In resistant strains, the bacteria are able to produce penicillin-degrading β-lactamases or have developed modified transpeptidases to which penicillins cannot bind anymore.[29] While biologists identified further β-lactam antibiotics from the penicillin and cephalosporin families, chemists investigated synthetic routes to β-lactam antibiotics. The first total synthesis of penicillin V (**1.11**) by Sheehan and co-workers was reported in 1952.[30] The synthesis of all stereoisomers was reported, and the proposed structure could be confirmed experimentally. Furthermore, the synthesis indicated that the site most amenable for modification was the amide side chain.

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[24] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *Tetrahedron* **1963***, 19,* 247; E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, R.B. Woodward, *J. Am. Chem. Soc.* **1956**, *78*, 3087; R. B. Woodward, *Pure & Appl. Chem*. **1968**, *17*, 519; R. B. Woodward, *Pure & Appl. Chem*. **1971**, *25*, 283; R. B. Woodward, *Pure & Appl. Chem*. **1973**, *33*, 145; A. Eschenmoser, C. E. Wintner, *Science* **1977**, *196*, 1410.

[25] C. H. Steffee, *N.C.Med. J.* **1992**, *53,* 308; A. Fleming, *Br. J. Exp. Pathol*. **1929**, *10*, 226; R. Hare, *Med. His*. **1982**, *26*, 1.

[26] E P. Abraham, E. Chain, C. M. Fletcher, *Lancet* **1941**, *16*, 177; D. Crowfoot, C. W. Bunn, B. W. Rogers-Low, A. Turner-Jones, "*X-ray crystallographic investigation of the structure of penicillin*" in Clarke, H. T.; Johnson, J. R.; Robinson, R. (ed). *Chemistry of Penicillin*. **1949**, Princeton University Press, Princeton.

[27] E. P. Abraham, G. G. F. Newton, *Biochemical Journal,* **1961***, 79*, 377.

[28] K. F. Kong, L. Schneper, K. Mathee, *Acta Pathol. Microbiol. Immunol. Scand.* **2010**, *118*, 1.

[29] K. Lewis, *Nat. Rev. Drug Discov*. **2013**, *12*, 371.

[30] J. C. Sheehan, K. R. Henery-Logan, *J. Am. Chem. Soc.* **1957**, *79*, 1262.


**Figure 1.3**: Collection of *Penicillium* molds (left) and an original mold sample from Alexander Fleming (right).[31]

This synthesis can also be seen as one of the earlier examples of biomimetic synthesis, as the side chains are introduced *via* acylation of the amide in the last steps similar to the biosynthesis of penicillins.[32] The key intermediate in Sheenan's synthesis is (+)-6-aminopenicillanic acid (6-APA) containing the penicillin core structure (**1.12**, Figure 1.4). In 1959, researchers at Beecham reported the isolation of 6-APA from penicillin fermentation mold,[33] and the synthesis of structural analogs of natural penicillins started from this intermediate. By simple acylation of the primary amino group of the β-lactam a myriad of analogs could be synthesized and their biological activity compared with other penicillins. These new semi-synthetic penicillin analogs could be fine-tuned to fulfill specific demands, such as lactamase stability, improved uptake and metabolic stability.[34] The knowledge gained from penicillins could then be applied to the cephalosporin class of β-lactam antibiotics. Cephalosporin C (**1.14**) was isolated in 1961 and its core structure 7-aminocephalosporanic acid (7-ACA, **1.13**, Figure 1.4), also proved to be amenable in the semi-synthesis of antibiotic cephalosporin derivatives.[35] The development of penicillins and cephalosporins as antibacterial drugs helped to establish new methodologies in biochemistry and drug discovery.

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[31] http://en.wikipedia.org/wiki/Penicillium#/media/File:Ascomycetes.jpg; Photo by: Dr. David Midgley Cultures: Dr. David Midgley, University of Sydney, Australia, Creative Commons BY-SA 2.5 license; http://commons.wikimedia.org/wiki/File:Sample_of_penicillin_mould_presented_by_Alexander_Fleming_to_Douglas_Macleod,_1935_(9672239344).jpg; Science Museum Photo Studio; Science Museum London, Creative Commons BY-SA 2.0 license.
[32] A. Brakhage, P. Spröte, Q. Al-Abdallah, A. Gehrke, H. Plattner, A. Tüncher, *Advances in Biochemical Engineering*, **2004**, Springer Berlin; C. J. Schofield, J. E. Baldwin, M. F. Byford, I. Clifton, J. Hajdu, C. Hensgens, P. Roach, *Curr. Op. Struct. Biol.* **2004**, *7*, 857.
[33] F. R. Batchelor, F. P. Doyle, J. H. C. Nayler, G. N. Rolinson, *Nature* **1959**, *183*, 257.
[34] A. M. Hujer, M. Kania, T. Gerken, V. E. Anderson, J. D. Buynak, X. Ge, P. Caspers, M. G. P. Page, L. B. Rice, R. A. Bonomo, *Antimicrob. Agents Chemother.* **2005**, *49*, 612.
[35] J. M. T. Hamilton-Miller, *Int. J. Antimicrob. A.* **2008**, *31*, 189.

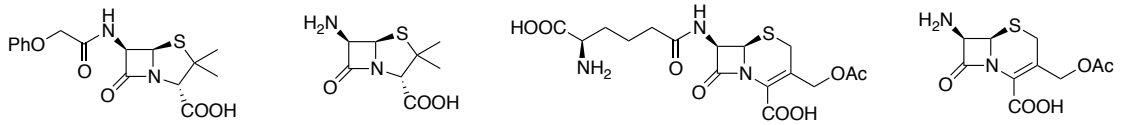



**Figure 1.4**: Structures of penicillins (left) and cephalosporins (right).

The controlled variation of fermentation conditions led to the isolation of new structures, which helped to elucidate the mechanisms of action of the β-lactam antibiotics in return. These are also some of the earliest examples of a drug accessed by fermentation of a fungi culture, and the identification and genetic modification of suitable fungal strains was unprecedented at the time.[36] From a total synthesis point of view, penicillins and cephalosporin's were formidable targets due to their complex structure. As in the case of paclitaxel (*vide infra*), the total syntheses were not able to compete with the fermentation process in terms of yield, but proved indispensable for the structural elucidation and mode of action investigations of the natural products. The large-scale production of 6-APA (**1.12**) and 7-ACA (**1.14**) gave rise to early examples of thorough structure-activity relationship (SAR) studies, a method that is now standard in medicinal chemistry. It can be argued that the greatest strengths of total synthesis are characterized by interplay with other disciplines, but foremost biology, where the coalescence of the research fields gives rise to synergies to a sum much greater than its individual parts.

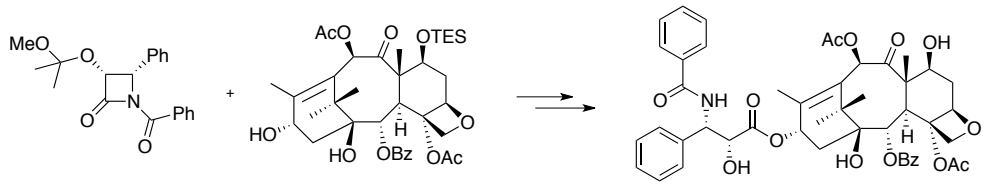
**Figure 1.5**: Pacific yew with characteristic berries (left) and debarking of the trunk (right).[37]

[36] H. A. Roslan, C. S. Ngo, S. Muid, *J. Cell Mol. Biol.* **2010**, *7,* 13.
[37] http://commons.wikimedia.org/wiki/File:Taxus_brevifolia_Blue_Mts_WA.jpg, Jason Hollinger, Creative Commons licence CC BY 2.0;
http://en.wikipedia.org/wiki/Paclitaxel#/media/File:Yew_bark_Taxol_PD.jpg; cancer.gov, Public Domain.

In 1963, a bioactivity-guided plant isolation program of the US government revealed extracts of the pacific yew *Taxus brevifolia* to possess anti-tumor activity (Figure 1.5).[38] By 1968, the active compound had been purified and the structure of paclitaxel (**1.17**) was assigned in 1971 ( Scheme 1.4).[39] Clinical trials conducted in the 1980s led to the FDA approval of paclitaxel (**1.17**) as a treatment of several cancers, such as ovarian, breast, and lung cancer.[40] Paclitaxel (**1.17**) was found to act as a microtubule-stabilizing agent and affects the cytoskeletal system. It blocks mitosis and arrests the uncontrolled cell division of the cancer cells.[41] Paclitaxel (**1.17**) was mainly extracted from the bark of the yew. Initial clinical trials in the 1980s required several tons of yew bark. This posed a threat to the ecosystem, as the plant is rather slow growing and killed during bark harvest (Figure 1.5, right). The initial isolation method gave only about 10 g of pure paclitaxel (**1.17**) from 1,200 kg of bark, and a typical treatment requires about 2 g of the drug per patient. Current annual demand is in the range of 200 kg per year (50,000 treatments) and rising.[42] The intricate structure of paclitaxel proved to be a challenging target for synthetic chemists, and indeed since the first syntheses by the groups of Holden and Nikolaou in 1994, several others have been reported.[43] While these syntheses cannot compete with the extraction route in terms of yield, they provided essential information for the production of paclitaxel on a commercial scale. One of these critical findings was the use of the Ojima lactam **1.15**[44] for the introduction of the side chain to the tetracyclic 10-deacetylbaccatin III derivative **1.16**. Indeed, most of the total syntheses mentioned above rely on this method, and so did the first semi-synthetic route to paclitaxel developed by Holton and commercialized by Bristol-Myers Squibb

[38] G. M. Cragg, *Med. Res. Rev.* **1998**, *18*, 315.
[39] M. Wani, H. Taylor, M. Wall, P. Coggon, A. McPhail , *J. Am. Chem. Soc.* **1971***, 93,* 2325.
[40] L. J. Cseke, A. Kirakosyan, P. B. Kaufmann, S. L. Warber, J. A. Duke, H. L. Brielmann, *Natural Products from Plants*, **2006**, Taylor and Francis, Boca Raton.
[41] G. A. Orr, P. Verdier-Pinard, H. McDaid, S. B. Horwitz, *Oncogene* **2003**, *22*, 7280.
[42] P. M. Dewick, *Medicinal Natural Products:A Biosynthentic Approach* **2002**, John Wiley and Son, West Sussex.
[43] R. A. Holton, C. Somoza, H. B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc.* **1994**, *116,* 1597; K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, *Nature* **1994**, *367,* 630; S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, M. J. Di Grandi, *J. Am. Chem. Soc.* **1996,** *118,* 2843; P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. G. Marquess, P. L. McGrane, *J. Am. Chem. Soc.* **1997**, *119*, 2757; K. Morihira, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, I. Kuwajima, *J. Am. Chem. Soc.* **1998**, *120*, 12980.
[44] I. Ojima, I. Habus, M. Zhao, M. Zucco, Y. H. Park, C. M. Sun, T. Brigaud, *Tetrahedron* **1992**, *48*, 6985.

from 1993 onwards.[45] The advantages of using derivative **1.16** as an advanced intermediate are twofold: 10-deacetylbaccatin (precursor of **1.16**) is found in the more abundant European yew (*Taxus baccata*) and in a higher concentration than paclitaxel, and the process is sustainable, as only twigs and leaves are used for the extraction, which regrow after a season. This rendered the approach more environmentally friendly and cost effective. Since 2004, the semi synthetic route has been replaced by a plant-cell fermentation process, where paclitaxel is directly extracted from a fermentation broth of *Taxus chinensis* cells.[46]




**1.15** **1.16** paclitaxel (**1.17**)

**Scheme 1.4**: Industrial semi-synthetic route to paclitaxel (**1.17**) by Bristol-Myers Squibb.

The development of paclitaxel into a drug illustrates the advantage of using organic synthesis to produce natural products. While total synthesis could not compete with the extraction route in terms of yield in this case, isolated natural products often are extremely scarce. Reasons for this include that the samples are hard to obtain (*e.g.* from marine environment), or general rarity of the specimen in the biosphere. The production of secondary metabolites is also highly dependent of environmental factors such as climate, pH, nutrient supply and can render repeated isolation difficult.[47] Total synthesis can turn a '*once in a lifetime*'-isolation of a small amount of a natural product into a reproducible route to the target compound. As absolute structural determination is difficult with only small quantities of substance available, total synthesis often serves as a final proof in structural assignment. As the commercial semi-synthetic route to paclitaxel illustrates, the combination of total synthesis with a suitable precursor obtained from natural sources can give much more ecologically and economically sustainable routes to a target.

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[45] J. Goodman, V. Walsh, *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-Cancer Drug*, **2001**, Cambridge University Press, Cambridge.
[46] P. G. Mountford, Green Chemistry in the Pharmaceutical Industry, **2010**, Wiley-VCH, Weinheim.
[47] D. J. Kliebenstein, *Plant, Cell Environ.,* **2004**, *27*, 675; A. Ramakrishna, G. A. Ravishankar, *Plant Signal. Behav.* **2014**, *6*, 1720.

## 1.4 The Educational Value of Total Synthesis

While the many medicinal, ecological and economical benefits have been highlighted in the previous section, the educational value of total synthesis for chemistry students cannot be neglected and will be briefly discussed in this section.

Total synthesis starts by choosing a suitable target. This usually involves the thorough literature study of total syntheses of related natural products, if there are any. The student thereby gains an understanding of the research field and the key challenges involved, and this allows the student to assess their own intellectual- and practical capabilities with respect to the task. Once a target is chosen, the next step is the retrosynthetic analysis. This usually involves several reiterations, and often the student has to choose between a more novel, risky and challenging route and a more conventional, but "safer", route. During the process, the student already gains a greater theoretical knowledge about the general reactivity of the planned intermediates and the corresponding synthetic transformations. This stage also promotes communicational skills by scientific discussions with more experienced co-workers about the envisaged route. After a route has been decided upon, the student bears the (often unforeseeable) consequences and enters the next stage of performing actual synthesis.

The most apparent gain of knowledge from the second stage is of practical nature. Total synthesis usually involves a wide range of chemical reactions, and the student thereby learns how to handle reactive reagents, quenching and disposal of reactive or toxic materials, and the proper setup of the reaction apparatuses. Sooner than later, the student will encounter a step in the sequence which will fail to deliver acceptable yield, purity, selectivity or poses other challenges.

It his here where one of the great values of total synthesis emerges: the art of scientific and creative problem solving. The scientific aspect forms the backbone of the problem solving process; it is the rigorous monitoring and variation of reaction parameters usually in reference to the relevant literature to overcome the synthetic challenge. The ability to develop and conduct a methodical plan for problem solving is fostered in this process. The creative aspect of the problem solving often involves the application of an unconventional or questionable concept or methodology to the problem at hand, and it is

undoubtedly here where greatest sources of satisfaction and inspiration of total synthesis lie.

Of course, not all encountered problems can be solved to satisfaction on every level, and the student eventually has to re-evaluate the possible alternatives in a synthetic route to circumvent the barriers blocking progress. With the experience gained from previous work, the student is ready for the next iteration of observing, learning and reflection on the process.

During this practice outlined above, the student will learn to deal with the inevitable failure and rejection of total synthesis, and will hopefully be able to observe the vanishing of barriers and the emergence of stepping-stones. Therefore, total synthesis is not only a great practice of mastering the intellectual and experimental challenges of organic chemistry, but also can be a way towards personal growth of the student.

## 1.5 Conclusions and Outlook

In this chapter, we have briefly touched upon the several influences natural products had on human society. The historic examples of indigo dye (**1.03**) and cetyl palmitate (**1.04**) illustrate the great benefits for the eco system by replacing natural sources with synthetic materials. The Baeyer synthesis of indigo at BASF is an early example of the industrial production of a compound previously obtained from natural sources.

The more modern example of the Aspirin (**1.08**) synthesis demonstrates the power of organic chemistry in drug development, where an easily introduced acetyl group greatly reduced undesired side effects and improved efficacy of the drug. It also is a prime example of drug discovery from a biological source, as was the isolation and structural assignment of quinine (**1.10**) from *Cinchona* bark. The 1944 formal synthesis of compound **1.10** by Woodward and Doering is now regarded as a milestone in total synthesis. This synthesis and later works by Woodward pushed the boundaries of synthetic organic chemistry, and today even the most complex molecules seem to be within reach given the required expertise, funding and time.[48]

[48] K. C. Nicolaou, R. J. Aversa, *Isr. J. Chem.* **2011**, *51*, 359; K. C. Nicolaou, K. P. Cole, M. O. Frederick, R. J. Aversa, R. M. Denton, *Angew. Chem. Int. Ed.* **2007**, *46*, 8875; K. C. Nicolaou, M. O. Frederick, A. C. B. Burtoloso, R. M. Denton, F. Rivas, K. P. Cole, R. J. Aversa, R. Gibe, T. Umezawa, T. Suzuki, *J.*

The discovery of penicillin opened new ways for the treatments of otherwise lethal bacterial infections and is a great example of the synergy between organic synthesis and biology. Thorough optimization led to the development of industrial scale fermentation of penicillins, which could then be further functionalized by chemical means to form structural analogs. This provided material for SAR studies to investigate biochemical pathways.

The account of paclitaxel (**1.17**) from a crude extract of yew bark to a prestigious total synthesis target and a top selling anti-cancer drug illustrates the scale to which drug discovery programs might develop. The account also demonstrates that the benefits of total synthesis are often not immediately apparent, but might prove beneficial in another context. An example of this is the total synthetic efforts of the Holton group, which eventually culminated in an industrial production of paclitaxel *via* semi-synthesis from the more abundant advanced intermediate, 10-deacetylbaccatin, extracted from European yew. This process has then been replaced by a plant cell fermentation process to an even greater relief of the eco system. Once again the greatest merits of total synthesis was achieved in synergy with biological methods.

The last section discussed the great value of total synthesis for the education of students. Total synthesis is a great environment for acquiring deep and diverse knowledge of synthetic transformations and practical execution in the lab. Methodical and creative problem-solving processes are among the key aspects to be learned.

Looking forward, the rise and fall in popularity of combinatorial chemistry or high throughput screening have shown that the "next big thing" in organic and medicinal chemistry is hard to predict, and that encouraging initial results might not stand the test of time.[49] A statement about the required foundation for a philanthropic and charitable development of organic chemistry and the pharmaceutical industry is more easily made. In many of the largest pharmaccutical companies, the expenses on marketing surpass the

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*Am. Chem. Soc.* **2008**, *130*, 7466; K. C. Nicolaou, P. Heretsch, T. Nakamura, A. Rudo, M. Murata, K. Konoki, *J. Am. Chem. Soc.* **2014**, *136*, 16444; K. C. Nicolaou, R. J. Aversa, J. Jin, F. Rivas, *J. Am. Chem. Soc.* **2010**, *132*, 6855.

[49] T. Kodadek, *Chem. Commun.* **2011**, *47*, 9757; J.-Y. Ortholand, A. Ganesan, *Curr. Opin. Chem. Biol.* **2004**, *8*, 271; H. Kubinyi, *Nat. Rev. Drug Discov.* **2003**, *2*, 665.

investment in research and development.[50] In combination with questionable handling of patent law,[51] this sheds a negative light on the industry. Investment into basic research facilities, in industry or academia, still seems to be a valuable approach for a steady development of new discoveries and drugs beneficial for society, both in an economically valuable and ethically justifiable fashion.

[50] https://openpaymentsdata.cms.gov/; http://www.washingtonpost.com/blogs/wonkblog/wp/2015/ 02/11/ big-pharmaceutical-companies-are-spending-far-more-on-marketing-than-research/; accessed 07.4.2015.
[51] S. Kadidal, *IDEA* **1996**, 7, 371; T. Caulfield, T. Bubela, C. J. Murdoch, *Genet. Med.* **2007**, *9*, 850; J. M. Mueller, *N. Engl. J. Med.* **2007**, *356*, 541

# 2 Total Synthesis of (–)-Pyridovericin

## 2.1 Alzheimer's Disease – a Neurodegenerative Disorder

During the course of the 20th century, the average life expectancy in developed regions has increased substantially.[52] In parallel, the occurrence of neurodegenerative diseases is now much more common, as these diseases are mostly prevalent in the elderly. Examples of neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). The common pathology observed in the aforementioned diseases is the gradual loss and degradation of neuronal structure and function.[53] As of today, there is no cure for any neurodegenerative disease, and treatments are of a palliative nature. The following section will discuss AD as one of the most prominent and intensively investigated examples of a neurodegenerative disease. German psychiatrist Alois Alzheimer reported the first case of AD in 1907.[54] Since then, the disorder has become widespread in aging, developed societies. Estimations indicate that the disease affects 5% of 65 year olds,[55] and that this number increases to about 40% for 80 year olds.[56]

The underlying intricate mechanisms of the disease have been the subject of great discussion in the scientific community. Already in 1911, Alois Alzheimer reported the observation of neurofibrillary anomalies in the brains of diseased patients.[57] A hundred years later, protein aggregation and plaque formation are recognized as one of the hallmarks of neurodegenerative diseases and AD especially. In Alzheimer patients, the plaque consists of extracellular aggregated amyloid β (Aβ) protein.[58] Aβ protein is formed by proteolysis of amyloid β precursor protein (APP) by the proteins β- and γ-secretase.[59] The primary function of APP is not known, but the membrane protein is mainly found in neurons. The released Aβ monomers initially form oligomers, which then aggregate further to form the Aβ plaque (Figure 2.1). The formation of Aβ plaque

[52] J. Oeppel, J. W. Vaupel, *Science*, **2002**, *296*, 1031.
[53] S. Sheikh, Safia, E. Haque, S. S. Mir, *J. Neurodeg. Dis.* **2013**, *2013*, 1.
[54] A. Alzheimer, *Zeitschrift für Psychiatrie und Psychisch-gerichtliche Medizin* **1907**, *64*, 146.
[55] R. Bullock, *Expert. Opin. Investig. Drugs* **2004**, *13*, 303.
[56] E. Forsyth, P. D. Ritzline, *Phys Ther.* **1998**, *78*, 1325.
[57] A. Alzheimer, *Zeitschrift für die Gesamte Neurologie und Psychiatrie* **1911**, *4*, 356.
[58] D. J. Selkoe, *Neuron* **1991**, *6*, 487.
[59] J. Hardy, D. J. Selkoe, *Science* **2002**, *297*, 353.

has been shown to cause neuronal inflammation, eventually leading to programmed cell death and loss of neuronal structure and function.[60] However, some studies argue that the Aβ plaque merely acts as a reservoir for the smaller Aβ oligomers, which themselves have been shown to be neurotoxic.[61]

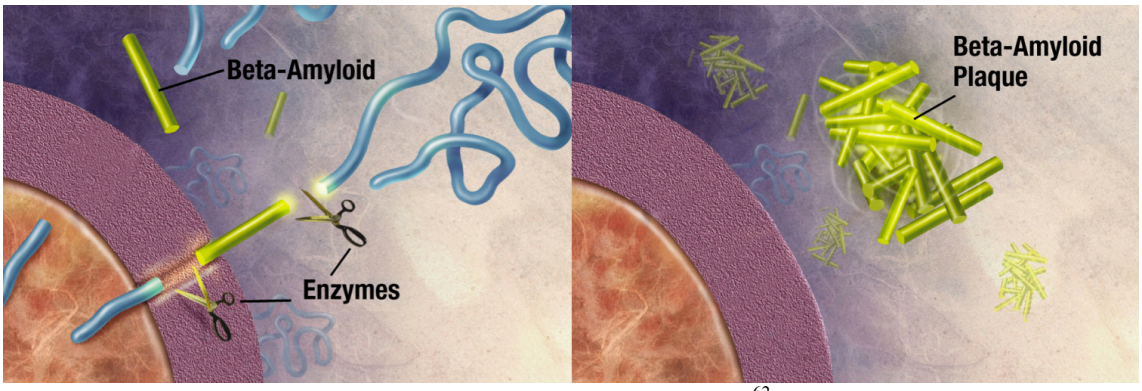


**Figure 2.1**: Proteolysis of APP (left) to give Aβ plaque (right).[62]

A second common pathology found in AD patients is the formation of aggregates of hyperphosphorylated tau protein.[63] Tau is a microtubule stabilizing protein. Microtubules are key structural elements of cells forming the cytoskeleton.[64] When tau is excessively phosphorylated, it detaches from the rest of the microtubule forming tau oligomers. In the process, the microtubules start to disintegrate and the neuron looses its cytoskeleton, leading to cell death.[65] Underlying these biomolecular irregularities are several genetic mutations associated with AD. So far, the identified genetic mutations have only been found to be associated with Aβ overexpression in mutations of the genes encoding APP and presinilins 1 and 2.[66]

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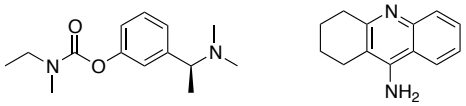
[60] C. J. Pike, D. Burdick, A. J. Walencewicz, C. G. Glabe, C. W. Cotman, *J. Neurosci.* **1993**, *13*, 1676; A. Lorenzo, B. A. Yankner, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 12243.
[61] D. M. Hartley, D. M. Walsh, C. P. Ye, T. Diehl, S. Vasquez, P. M. Vassilev, *J. Neurosci.* **1999**, *19,* 8876; M. P. Lambert, A. K. Barlow, B. A. Chromy, C. Edwards, R. Freed, M. Liosatos, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 6448.
[62] http://upload.wikimedia.org/wikipedia/commons/0/0d/Amyloid_03big1.jpg; used under permission of the public domain license.
[63] A. C. Alonso, T. Zaidi, I. Grundke-Iqbal, K. Iqbal, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 5562, G. T. Bramblett, M. Goedert, R. Jakes, S. E. Merrick, J. Q. Trojanowski, V. M. Lee, *Neuron* **1993**, *10*, 1089.
[64] G. Lindwall, R. D. Cole, *J. Biol. Chem.* **1984**, *259*, 5301.
[65] M. Mandelkow, E. Mandelkow, *Trends Cell Biol.* **1998**, *8*, 425.
[66] W. J. Strittmatter, A. M. Saunders, D. Schmechel, M. Pericak-Vance, J. Enghild, G. S. Salvesen, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1977.

Although these mutations not necessarily evoke AD, they have been identified as risk factors.[67]

While this was a general overview over the most prevalent processes involved in AD, the complexity and scale of the research field would exceed the scope of this introduction, but several reviews are available for further reading.[68] The next section briefly discusses possible therapeutic targets of AD.

## 2.2 Therapeutic Targets of Alzheimer's Disease




**2.01** **2.02**

**Figure 2.2**: AChE inhibitors Rivastigmine (**2.01**) and Tacrine (**2.02**).

The currently available medications for the treatment of AD are acetylcholinesterase (AChE) inhibitors, such as Rivastigmine (**2.01**) or Tacrine (**2.02**, Figure 2.2). First reports of an unbalanced acetylcholine metabolism in AD date back to the 1970s,[69] and while AChE inhibitors have been shown to delay the course of the disease, unfortunately the effects seem to be marginal.[70] The elucidation of the role of Aβ plaque, tau aggregation and genetic risk factors gave rise to several new therapeutic approaches, which have been proposed and tested.

In the case of Aβ plaque formation, several pathways are potentially amenable for intervention. These involve for example the inhibition of β– and γ– secretase, giving lower concentrations of Aβ monomers.[71] The inhibition of Aβ plaque formation was

[67] D. J. Selkoe, *Neurol. Clin*. **2000**, *18*, 903.
[68] H. W. Klafki, M. Staufenbiel, J. Kornhuber, J. Wiltfang, *Brain* **2006**, *129*, 2840; T. E. Golde, *J. Clin. Invest.* **2003**, *111*, 11; Y. Huang, L. Mucke, *Cell* **2012**, *148*, 1204.
[69] D. M. Bowen, C. B. Smith, P. White, A. N. Davison, *Brain* **1976**, *99*, 459; E. K. Perry, R. H. Perry, G. Blessed, B. E. Tomlinson, *Lancet*, **1977**, *1*, 189.
[70] E. Scarpini, P. Scheltens, H. Feldman, *Lancet Neurol.* **2003**, *2*, 539.
[71] I. Hussain, D. Powell, D. R. Howlett, D. G. Tew, T. D. Meek, C. Chapman, *Mol. Cell. Neurosci.* **1999**, *14*, 419; E. Siemers, M. Skinner, R. A. Dean, C. Gonzales, J. Satterwhite, M. Farlow, *Clin. Neuropharmacol.* **2005**, *28*, 126.

also investigated,[72] and seminal immunotherapeutic approaches by immunization with Aβ gave promising results.[73]

As mentioned previously, hyperphosphorylation of tau gives rise to the decomposition of microtubule and collapse of the cytoskeleton of the neuron. Tau kinase, the enzyme transferring the phosphate group to the tau protein, is therefore currently under investigation as a therapeutic target,[74] as is the activation of tau phosphatase, which could reverse the process and could cause the degradation of tau aggregates by dephosphorylation.[75]

Other compound classes under investigation are anti inflammatory drugs[76] and cholesterol regulating agents, as it has been shown that the proteolysis of APP to Aβ is dependent of cholesterol plasma levels.[77]

The described therapeutic approaches all focus on the inhibition of destructive biochemical processes. However, the cellular repair of damaged nerve tissue would certainly be beneficial for successful treatment of neurodegenerative disorders. Many natural products have shown to possess neuritogenic activity in cell and animal models,[78] and in the following section our studies of truncated neuritogenic natural product analogs are presented.

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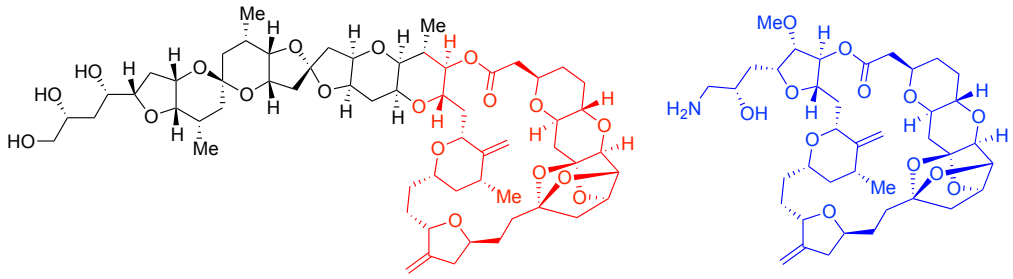
[72] M. Citron, *Nat. Rev. Neurosci.* **200,** *5*, 677; C. S. Atwood, R. D. Moir, X. Huang, R. C. Scarpa, N. M. Bacarra, D. M. Romano, *J. Biol. Chem.* **1998**, *273*, 12817.
[73] F. Bard, C. Cannon, R. Barbour, R. L. Burke, D. Games, H. Grajeda, *Nature Med.* **2000**, 6*,* 916.
[74] S. Le Corre, H. W. Klafki, N. Plesnila, G. Hubinger, A. Obermeier, H. Sahagun, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 9673; W. Noble, E. Planel, C. Zehr, V. Olm, J. Meyerson, F. Suleman, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 6990.
[75] L. F. Lau, J. B. Schachter, P. A. Seymour, M. A. Sanner, *Curr. Top. Med. Chem.* **2002**; *2.* 395; K. Iqbal, I. Grundke-Iqbal, *Curr. Drug Targets* **2004**, *5*, 495.
[76] C. A. Szekely, J. E. Thorne, P. P. Zandi, M. Ek, E. Messias, J. C. Breitner, *Neuroepidemiology,* **2004**, *23*, 159.
[77] K. Fassbender, M. Simons, C. Bergmann, M. Stroick, D. Lutjohann, P. Keller*, Proc. Natl. Acad. Sci. USA* **2001**; *98*, 5856; L. T. Friedhoff, E. I. Cullen, N. S. Geoghagen, J. D. Buxbaum, *Int. J. Neuropsychopharmacol.* **2001**, *4*, 127.
[78] V. Sofiyev, G. Navarro, D. Trauner, *Org. Lett.* **2008**, *10*, 149; T. Itoh, M. Kinoshita, S. Aoki, M. Kobayashi, *J. Nat. Prod.* **2003**, *66*, 1373; P.-Y. Dakas, J. A. Parga, S. Höing, H. R. Schöler, J. Sterneckert, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 9576.

## 2.3 Truncation of Natural Products

As described in chapter 1, biologically active compounds from natural sources have laid the foundation of human medicine throughout history. With the development of advanced analytical and synthetic methodologies in the 20th century, the identification and preparation of natural products and analogs has become more feasible. Combined with the advances in chemical biology for the biological evaluation of the compounds, several concepts, such as structure-activity relationships (SAR), function-oriented synthesis (FOS)[79] or diversity-oriented synthesis (DOS),[80] provide now a solid foundation for the identification and structural optimization of bioactive compounds. One focus of our research is the truncation of natural products, a concept that involves the preparative and structural simplification of a target structure while retaining or even improving its biological activity. Several reviews on the subject are also available.[81]



**2.03** **2.04**

**Figure 2.3**: Halochondrin B (**2.03**) and truncated analog eribulin (**2.04**).

A prominent example of a truncated natural product is halichondrin B (**2.03**) and its truncated analog eribulin (**2.04**) (Figure 2.3). Halochondrin B (**2.03**) is a polyether macrolide from marine sponges isolated by Umura (1986)[82] and Pettit (1991).[83] Initial biological studies showed that the compound possessed promising anti-tumor activities, and later investigations revealed the mechanism to involve the inhibition of tubulin polymerization and microtubule formation.[84] As the isolation of the compound from

[79] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40.
[80] D. S. Tan, *Nature Chem. Biol.* **2005**, *1*, 74.
[81] J.-Y. Wach, K. Gademann, *Synlett* **2012**, *2*, 163; E. Crane, K. Gademann, manuscript in preparation.
[82] D. Uemura, K. Takahashi, T. Yamamoto, C. Katayama, J. Tanaka, Y. Okumura, Y. Hirata, *J. Am. Chem. Soc.* **1985**, *107*, 4796; Y. Hirata, D. Uemura, *Pure Appl. Chem.* **1986**, *58*, 701.
[83] G. R. Pettit, C. L. Herald, M. R. Boyd, J. E. Leet, C. Dufresne, D. L. Doubek, J. M. Schmidt, R. L. Cerny, J. N. Hooper, K. C. Rutzler, *J. Med. Chem.* **1991**, *34*, 3339.
[84] K. L. Jackson, J. A. Henderson, A. J. Phillips, *Chem. Rev.* **2009**, *109*, 3044; R. L. Bai, K. D. Paull, C. L. Herald, L. Malspeis, G. R. Pettit, E. Hamel, *J. Biol. Chem.* **1991**, *266*, 15882.

biological matrices did not yield the required amounts for further clinical studies, several groups approached the total synthesis of target **2.03** and structural analogs thereof. The group of Kishi reported the first total synthesis of halichondrin B (**2.03**) in 1992,[85] but still the synthesis was not able to deliver substantial amounts of the target compound. In 2001, it was reported that the structural analog eribulin (**2.04**) possessed a similar biological profile to the parent molecule **2.03**,[86] and the synthetic route has been further optimized to a multi-kilogram scale.[87] Eribulin mesylate (Halaven) has recently been approved by the FDA for metastatic breast cancer.[88] This example clearly demonstrates the power of truncation of natural products, as totally synthetic halichondrin B will probably not be accessible in clinically useful quantities in the near future.

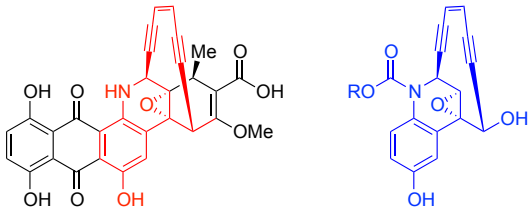



**Figure 2.4**: Dynemicin A (**2.05**) and truncated analog (**2.06**).

Dynemicin A (**2.05**) is another natural product that gave rise to bioactive truncated analogs such as **2.06** (Figure 2.4). The isolation of dynemicin A (**2.05**) was reported in 1989 by the group of Clardy.[89] Fermentation of *Micromonospora chersina* followed by bioassay-guided isolation gave compound **2.06**, bearing a characteristic strained 10-

[85] T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, M. C. Matelich, P. M. Scola, D. M. Spero, S. K. Yoon, *J. Am. Chem. Soc.* **1992**, *114*, 3162; T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, P. M. Scola, *Tetrahedron Lett.* **1992**, *33*, 1549; K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, P. M. Scola, S. K. Yoon, *Tetrahedron Lett.* **1992**, *33*, 1553.
[86] M. J. Towle, K. A. Salvato, J. Budrow, B. F. Wels, G. Kuznetsov, K. K. Aalfs, S. Welsh, W. Zheng, B. M. Seletsky, M. H. Palme, G. J. Habgood, L. A. Singer, L. V. Dipietro, Y. Wang, J. J. Chen, D. A. Quincy, A. Davis, K. Yoshimatsu, Y. Kishi, M. J. Yu, B. A. Littlefield, *Cancer Res.* **2001**, *61*, 1013.
[87] B. C. Austad, F. Benayoud, T. L. Calkins, S. Campagna, C. E. Chase, H. W. Choi, W. Christ, R. Costanzo, J. Cutter, A. Endo, F. G. Fang, Y. B. Hu, B. M. Lewis, M. D. Lewis, S. McKenna, T. A. Noland, J. D. Orr, M. Pesant, M. J. Schnaderbeck, G. D. Wilkie, T. Abe, N. Asai, Y. Asai, A. Kayano, Y. Kimoto, Y. Komatsu, M. Kubota, H. Kuroda, M. Mizuno, T. Nakamura, T. Omae, N. Ozeki, T. Suzuki, T. Takigawa, T. Watanabe, K. Yoshizawab, *Synlett* **2013**, *24*, 327.
[88] Eisai, E7389 Versus Treatment of Physician's Choice in Patients With Locally Recurrent or Metastatic Breast Cancer*,* ClinicalTrials.gov [Internet], Bethesda (MD): National Library of Medicine (US), 2006- [cited 2015 Jan 27]. Available from: https://clinicaltrials.gov/show/NCT00388726 NLM identifier: NCT00388726.
[89] M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Miyaki, T. Oki, H. Kawaguchi, G. D. Vanduyne, J. Clardy, *J. Antibiot.* **1989**, *42*, 1449; M. Konishi, H. Ohkuma, T. Tsuno,T. Oki, G. D. Vanduyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715.

membered ring with a 1,5-diyn-3-ene system. Seminal biological studies revealed the compound to be highly potent against several cancer cell lines. The intricate structure caused considerable synthetic effort in the community, and the first total synthesis of dynemicin A (**2.05**) by the Myers group was reported in 1995.[90] From a mechanistic point of view, it was found that the anthraquinone core intercalated with DNA, and it is proposed that the 1,5-diyn-3-ene system forms a phenyl diradical by a reaction cascade involving two one-electron reductions followed by tautomerization, epoxide opening and finally Bergman cyclization. The phenyl diradical then cleaves the 2-deoxyribose-phosphate backbone of the DNA, resulting in a double strand cleavage. Dynemicin A binds preferentially to B-DNA, and currently truncated analogs such as compound **2.06** are under investigation for treatment of various cancers.[91] While many analogs have been reported in the literature and their cytotoxic properties were studied, the hope is that a compound with a higher specificity for certain cancer cell lines is found, as the current analogs unfortunately also display high cytotoxicity towards healthy cells.

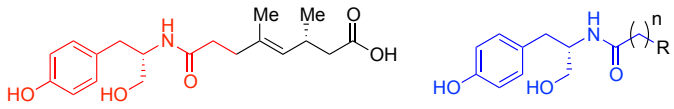



**Figure 2.5**: Farinosone C (**2.07**) and truncated analogs (**2.08-2.09**).

Examples by our group of a successfully truncated natural product with neuritogenic activity are the derivatives of farinosone C (**2.07**, Figure 2.5). Farinosone C (**2.07**) was first isolated by the group of Hamburger and showed neuritogenic activity in the *pheochromacytoma*-12 (PC-12) cell assay.[92] Biosynthetically, it was proposed that farinosone C (**2.07**) actually is a side product of the biosynthesis of the vast family of pyridone alkaloid natural products (see section 2.5), as the primary alcohol in compound **2.07** is unable to undergo the cyclization to form the pyridone. The proposed biosynthesis of the corresponding pyridone alkaloids requires a carboxylic acid in this

[90] A. G. Myers, M. E. Fraley, N. J. Tom, S. B. Cohen, D. J. Madar, *Chem. Biol.* **1995**, *2*, 33.
[91] J. A. Porco, F. J. Schoenen, T. J. Stout, J. Clardy, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 7410; K. C. Nicolaou, C. K. Hwang, A. L. Smith, S. V. Wendeborn, *J. Am. Chem. Soc.* **1990**, *112*, 7416; T. Nishikawa, M. Isobe, T. Goto, *Synlett* **1991**, 393; J. Taunton, J. L. Wood, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 10378; T. Y. Yoon, M. D. Shair, S. J. Danishefsky, G. K. Shulte, *J. Org. Chem.* **1994**, *59*, 3752; M. D. Shair, T. Y. Yoon, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **1995**, *34*, 1721; M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, *118*, 9509.
[92] Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li, M. Hamburger, *J. Nat. Prod.* **2004**, *67*, 1854.

position.[93] Farinosone C (**2.07**) was isolated from the entomopathogenic fungus *Paecylomyces farinosus*, and the total synthesis was concluded by our group in 2009 along with several structural analogs (**2.08** and **2.09**, Figure 2.5).[94] The stereodivergent approach allowed for assignment of the absolute configuration of the natural product, as well as truncation of the side chain. Biological evaluation in the PC-12 cell assay led to the identification of a truncated analog **2.09**, and further studies in collaboration with the Gertsch group indicated the $CB_1$ receptor as a possible target of truncated analog **2.09**.[95] This project also sparked our interest in the synthesis of pyridone alkaloids and their neuritogenic properties.

## 2.4 (–)-Pyridovericin – a Pyridone Alkaloid from the Entomopathogenic Fungus *Beauveria Bassiana*

Entomopathogenic fungi rely on a host insect for reproduction, to which they cause severe harm or death during the process. They have been shown to be a great source of biologically active natural products.[96] Their intricate multi-stage life cycle and its dependence on environmental factors is described in the next paragraphs.[97]

Generally, the long term persistence and infective fungal spores called conidia rest in the environment such as soil, a plant surface or in the rhizosphere (plant root system).[98] This period of the life cycle is called saprophytic phase, and the conidia can be spread by wind, rain or through contact with insects.[99] When the conidia come in contact with a host insect, they enter the body through the cuticle by a combination of mechanical force applied by the germ tube of the conidia and cuticle degrading enzymes such as chitinases and proteases.[100] Once the cuticle has been successfully penetrated, the fungus

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[93] K. L. Eley, L. M. Halo, Z. Song, H. Powles, R. J. Cox, A. M. Bailey, C. M. Lazarus, T. J. Simpson, *ChemBioChem* **2007**, *8*, 289.
[94] H. J. Jessen, D. Barbaras, M. Hamburger, K. Gademann, *Org. Lett.* **2009**, *11*, 3446.
[95] P. Burch, A. Chicca, J. Gertsch, K. Gademann, *ACS Med. Chem. Lett.* **2014**, *5*, 172.
[96] S. P. Putri, H. Kinoshita, F. Ihara, Y. Igarashi, T. Nihira, *J. Nat. Prod.* **2009**, *72*, 1544; D. Reimer, F. I. Nollmann, K. Schultz, M. Kaiser, H. B. Bode, *J. Nat. Prod.* **2014**, *77*, 1976; F. Grundmann, M. Kaiser, M. Schiell, A. Batzer, M. Kurz, A. Thanwisai, N. Chantratita, H. B. Bode, *J. Nat. Prod.* **2014**, *77*, 779.
[97] N. V. Meyling, J. Eilenberg, *Biological Control* **2007**, *43*, 145.
[98] A. E. Hajek, *Adv. Microb. Ecol*. **1997**, *15*, 193; S. Keller, G. Zimmerman, Insect-Fungus Interactions. 1989, Academic Press, London, UK.
[99] G. D. Inglis, M. S. Goettel, T. M. Butt, H. Strasser, Fungi as Biocontrol Agents. Progress,Problems and Potential, **2001**, CABI Publishing, pp. 23–69; R. M. Anderson, R. M. May, *Philos. Trans. R. Soc. Lond*. **1981**, *B 291*, 451.
[100] L. Duo-Chuan, *Mycopathologia* **2006**, *161*, 345.

forms a multicellular tissue of blastosphores, which infests the whole host through the haemocoel.[101] The fungal tissue secretes a wide range of bioactive compounds in the process, with toxins to weaken the host's immune system and antimicrobial compounds preventing secondary infections of competing microbes.[102]

As the fungus consumes the host's tissue for nutrients, several behavioral changes in host insects have been reported. In insects living in colonies, the abandonment of the hive has been reported, and it is speculated that this is a countermeasure against further spreading of the infection.[103] In some cases, the infection causes increased sexual attractiveness towards mates by up-regulation of pheromone production, helping the sporulating fungus to spread.[104] In many cases, the final and ultimately lethal phase of infection is accompanied by so called "classic summit disease", where the host relocates to a point of higher elevation, for example by moving to the soil surface in root feeding hosts or climbing on plant stems for superterranean insects. It is argued that this behavioral change is also a mechanism beneficial for the dispersion of fungal spores into the environment.[105] Finally, the host is completely consumed and covered by fungal tissue, and the last step of the reproductive cycle is the release of infective conidia from the fungal fruit body into the environment.

The elucidation of these fascinating biological interactions between fungi and host have led to application of entomopathogenic fungi as pest control agents, and the species *Beauveria bassiana* (*B.b.)* has gained special attention in this field.[106] This species is a fungus of the order hypocreales and has been shown to be able to infect over 700 different host species.

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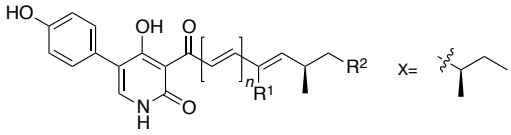
[101] R. A. Samson, H. C. Evans, J. P. Latgé, *Atlas of entomopathogenic fungi*, **1988**, Springer, Berlin.
[102] G. Zimmermann, *Biocontrol Sci. Tech*. **2007**, 17, 553.
[103] D. H. Oi, R. M. Pereira, *Fla. Entomol*. **1993**, *76*, 63; R. J. Milner, D. G. Holdom, T. R. Glare. *Entomol. Exp. Appl*. **1984**, *36*, 3.
[104] A. P. Möller, *Behav. Ecol. Sociobiol*. **1993**, *33*, 403; G. V. P. Reddy, M. J. Furlong, J. K. Pell, G. M. Poppy, *J. Invertebr. Pathol*. **1998**, *72*, 167; D. W. Watson, J. J. Petersen, *Biol. Control* **1993**, *3,* 22.
[105] H. C. Evans, *Insect-Fungus Interactions* **1989**, Academic, San Diego; P. I. Marikovsky, *Insect Soc*. **1969**, *9*, 173; K. Yamazaki, S. Sugiura, Y. Fukasawa, *Entomol. Sci*. **2004**, *7*, 219.
[106] N. V. Meyling, J. Eilenberg, *Biological Control* **2007**, *43*, 145; G. Zimmermann, *Biocontrol Science and Technology,* **2007**, *17*, 553.

The excessive use of chemical pest control agents has given rise to resistant insect strains, and the application of entomopathogenic fungi could prove a viable additional method for crop protection.[107] Several studies have shown that application of formulations of *B.b.* with or without additional pesticides has beneficial effects on pest mortality. Additionally, it should be mentioned that *B.b.* and related fungi have been reported to show essentially no toxicity whatsoever against vertebrates.[108]



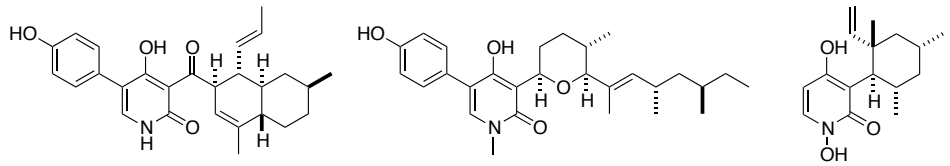

n = 2, $R^1$ = $CH_3$, $R^2$ = X: Militarinone D (**2.10**)
n = 3, $R^1$ = $CH_3$, $R^2$ = $CH_3$: Farinosone A (**2.11**)

**Figure 2.6**: Militarinone D (**2.10**) and farinosone A (**2.11**).

While the application of *B.b.* formulations is certainly attractive, the investigation of the biochemical mechanisms involved in infection has proven equally promising. The constant battle between the host and the fungi for survival and adaptation has been called an "*evolutionary arms race*",[109] and several key agents produced by the fungi have been identified and studied, such as cuticle degrading proteins or immunosuppressive agents.[110] This insight could give rise to the identification of new biochemical pathways amenable for pest control. Among the isolated compounds are also pyridone alkaloids, such as militarinone D (**2.10**) or farinosone A (**2.11**) (Figure 2.6).[111] While their exact role in the fungal interaction with the host is not yet clarified, they have certainly received considerable attention in the biological and chemical community, the results of which are presented in the next sections.

[107] V. Ambethgar, *J. Biopest.* **2009**, *2*, 177.
[108] P. A. Shah, J. K. Pell, *Appl. Microbiol. Biotechnol.* **2003**, *61*, 413; A. Shahid Ahmad, Q. Rao Abdul, A. Bakhsh, T. Husnain, *Arch. Biol. Sci.* **2012**, *64*, 21, M. A. Ansari, E. C. Pope, S. Carpenter, E.-J. Scholte, T. M. Butt, *PLoS ONE* **2011**, *6*, e16108.
[109] H. E. Roy, D. C. Steinkraus, J. Eilenberg, A. E. Hajek, J. K. Pell, *Annu. Rev. Entomol.* **2006**, *51*, 331.
[110] G. A. Amin, N. A. Youssef, S. Bazaid, W. D. Saleh, *Worldw. J. Microbiol. Biotechnol.* **2010**, *26*, 2263.
[111] Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li, M. Hamburger, *J. Nat. Prod*. **2004**, *67*, 1854; Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li, M. Hamburger, *J. Nat. Prod*. **2006**, *69*, 436; K. Schmidt, U. Riese, Z. Li, M. Hamburger, *J. Nat. Prod*. **2003**, *66*, 378; K. Schmidt, W. Günther, S. Stoyanova, B. Schubert, Z. Li, M. Hamburger, *Org. Lett*. **2002**, *4*, 197.

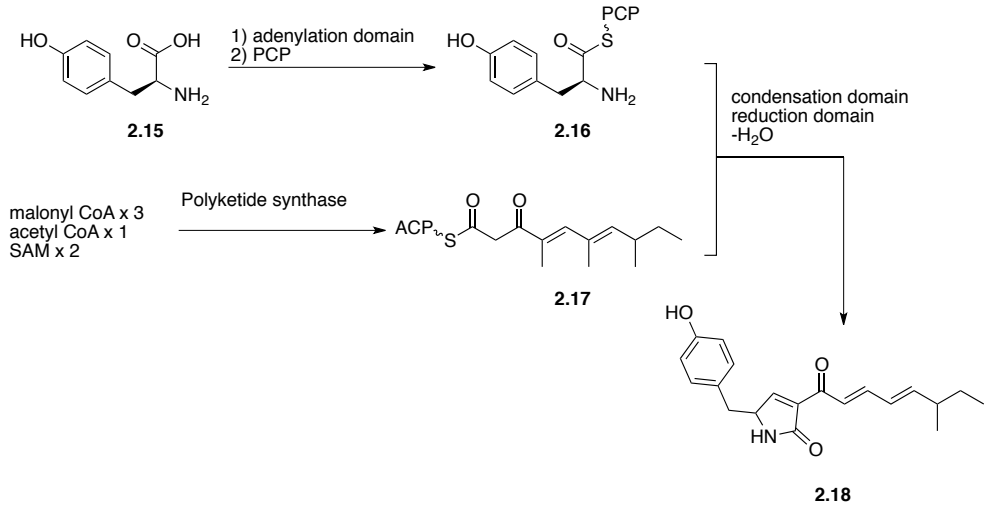
## 2.5 Occurrence, Classification and Biosynthetic Pathways of Pyridone Alkaloids



**2.12** **2.13** **2.14**

**Figure 2.7**: Representative members of the pyridone natural product family.

Pyridone alkaloid natural products are a vast and diverse class of mainly fungal metabolites.[112] Three selected members of the family are presented in Figure 2.7. The natural products can be further divided into three subclasses depending on their substitution pattern. The first class consists of 4-hydroxy-3-acyl substituted compounds, such as ilicicolin H (**2.12**). This group has received the greatest attention with respect to biosynthetic pathway investigation and total synthesis efforts. The second class has a 4-hydroxy-3-ether substitution pattern as in (+)-sambutoxin (**2.13**). The third class consists of natural products such as 8-methylpyridoxatin (**2.14**), bearing a 4-hydroxy-3-alkyl substituted 2-pyridone fragment.

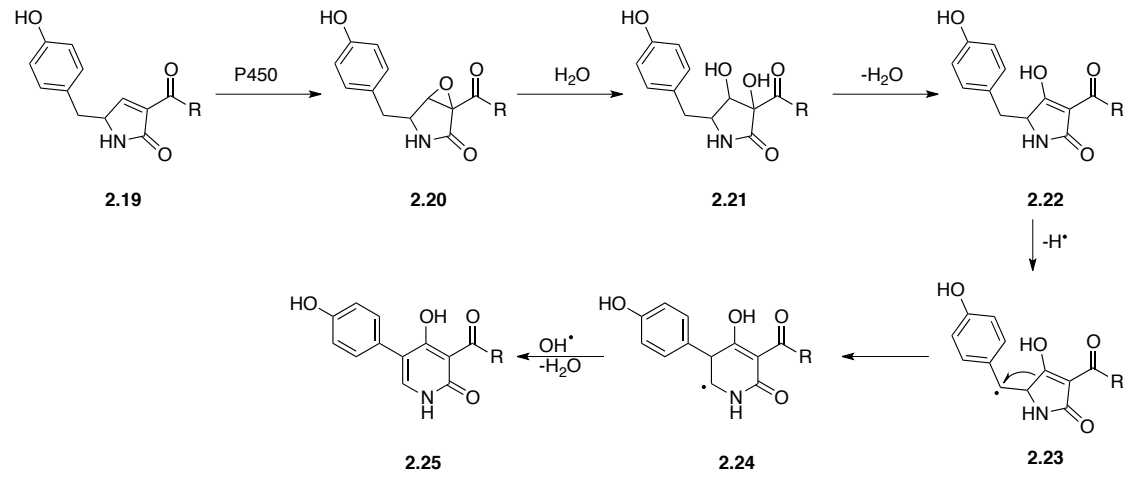



**Scheme 2.1**: Biosynthesis of pretenellin (**2.18**).

[112] H. J. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168.

Scheme 2.1 shows the biosynthetic pathway of pretenellin (**2.18**) as proposed by the Simpson group.[113] The pathway was elucidated by genome sequencing, knockout experiments and database comparison with similar non-ribosomal peptide synthetase (NRPS)-polyketide synthase (PKS) complexes. Initially, the activated polyene **2.17** is produced by a PKS. A NRPS affords the peptide carrier protein (PCP) bound tyrosine derivative **2.16**. The building blocks **2.16** and **2.17** are then condensed, the thioester is reduced and, upon elimination of water, pretenelin (**2.18**) is obtained.

In another study, the group further reported the biosynthesis of tetramic acid **2.19** and further skeletal oxidative rearrangements to form the characteristic 4-hydroxy-3-acyl-2-pyridone core of tenellin (**2.25**, Scheme 2.2). The process involves an initial oxidation of enone **2.19** to the epoxide **2.20** by cytochrome P450.[114] A sequential addition and elimination of water gives tetramic acid **2.21**. Hydrogen abstraction and rearrangement gives the radical **2.24**, which upon hydroxyl radical addition and elimination of water gives the natural product tenellin (**2.25**). In the next section, a few selected examples of total syntheses of 4-hydroxypyridone natural products will be discussed.

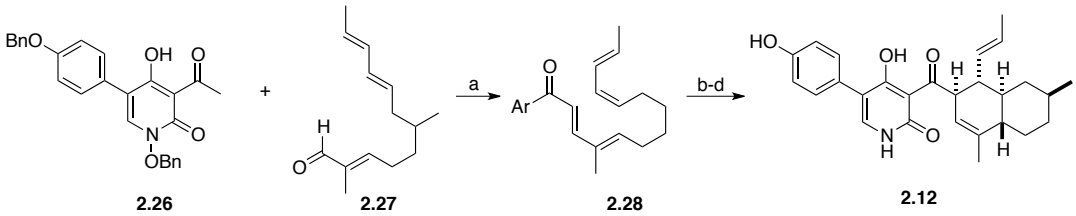



**Scheme 2.2**: Biosynthesis of tenellin (**2.25**).

[113] K. L. Eley, L. M. Halo, Z. Song, H. Powles, R. J. Cox, A. M. Bailey, C. M. Lazarus, T. J. Simpson, *ChemBioChem* **2007**, *8*, 289; Z. Song, R. J. Cox, C. M. Lazarus, T. J. Simpson FRS, *ChemBioChem* **2004**, *5*, 1196.
[114] L. M. Halo, M. N. Heneghan, A. A. Yakasai, Z. Song, K. Williams, A. M. Bailey, R. J. Cox, C. M. Lazarus, T. J. Simpson, *J. Am. Chem. Soc.* **2008**, *130*, 17988.

## 2.6 Previous Synthetic Studies on Pyridone Alkaloids

The synthesis of 4-hydroxypyridone natural products has been reviewed,[112] and this section will focus on representative examples from the three main groups described in section 2.5.




**2.26** **2.27** **2.28** **2.12**

**Scheme 2.3**: Racemic synthesis of ilicicolin H (**2.12**). a) KO*t*Bu, -40 °C, THF, 4 h, 72%; b) *o*-dichlorobenzene, reflux, 5 min, 80%; c) LDA, THF, -78 °C, 20 min, then HOAc–$H_2O$; d) $BCl_3$, DCM, -78 °C, 1 min, then MeOH, 60% over two steps.

Ilicicolin H (**2.12**) was isolated in 1971 from *Cylindrocladium ilicicola* and was found to possess antifungal and antibiotic properties.[115] The absolute configuration and the biosynthesis have also been investigated.[116] The Williams group reported a racemic synthesis of compound **2.12**[117] starting from the known advanced intermediate **2.26** (Scheme 2.3).[118] An aldol condensation between ketone **2.26** and aldehyde **2.27** using potassium *tert*-butanonlate gave enone **2.28**, which underwent a thermal Diels-Alder reaction[119] to establish the *trans*-decalin substituted side chain. Subsequent deprotection gave racemic ilicolin H (**2.12**).

(–)-Sambutoxin (**2.13**) was isolated in 1994,[120] and its enantiomer was synthesized in 2000 by Williams and co-workers (Scheme 2.4).[121] Isolated from *Fusarium sambucium*, the compound was found to cause toxic effects in rats. The intermediate **2.29** was synthesized *via* an asymmetric conjugate addition and *anti*-aldol reaction, and then the enolate of **2.29** added to aldehyde **2.30**. Fmoc deprotection caused spontaneous cyclization to form a dihydropyridone, which was then oxidized to give pyridone **2.32**.

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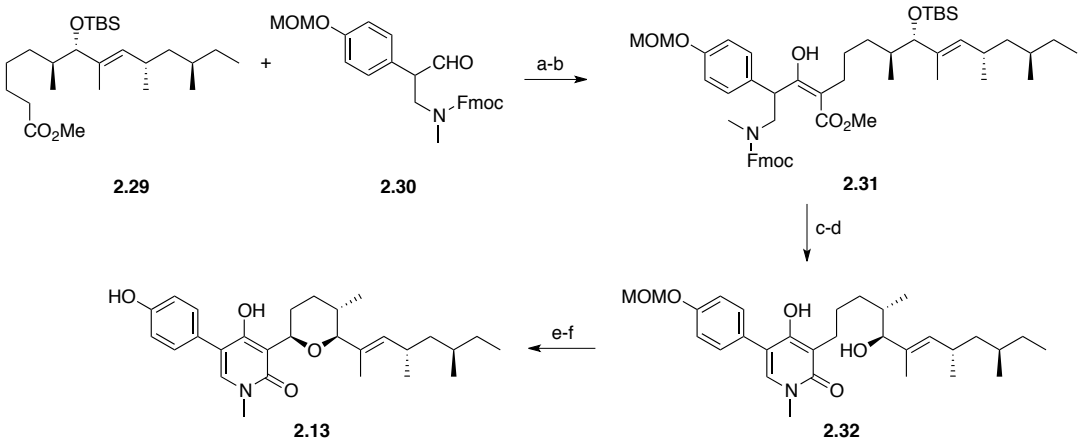
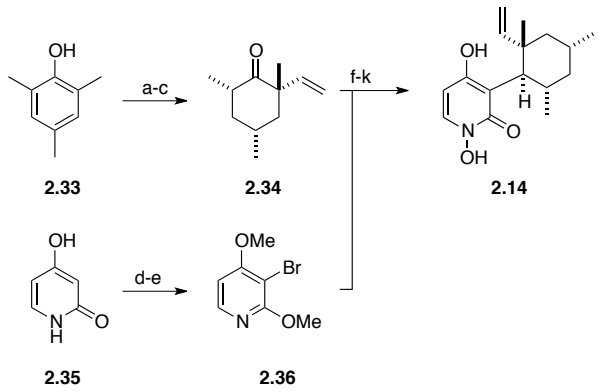
[115] S. Hayakawa, H. Minato and K. Katagiri, *J. Antibiot*. **1971**, *24*, 653.
[116] M. Matsumoto and H. Minato, *Tetrahedron Lett*. **1976**, *17*, 3827; M. Tanabe and S. Urano, *Tetrahedron* **1983**, *39*, 3569.
[117] D. R. Williams, M. L. Bremmer, D. L. Brown, J. D'Antuono, *J. Org. Chem*. **1985**, *50*, 2809.
[118] D. R. Williams, S.-Y. Sit, *J. Org. Chem*. **1982**, *47*, 2846.
[119] O. Diels, K. Alder, *Ann*. **1926**, *450*, 237; O. Diels, K. Adler, *Ann*. **1928**, *460*, 98; O. Diels, K. Alder, *Ber*. **1929**, *62B*, 2087; O. Diels, K. Alder, P. Pries, *Ber*. **1929**, *62B*, 2081.
[120] J.-C. Kim, Y.-W. Lee, *Appl. Environ. Microbiol*. **1994**, *60*, 4380; J.-C. Kim, Y.-W. Lee, H. T. Tamura, T. Yoshizawa, *Tetrahedron Lett*. **1995**, *36*, 1047.
[121] D. R. Williams, R. A. Turske, *Org. Lett*. **2000**, 2, 3217.




**Scheme 2.4**: Synthesis of (+)-sambutoxin (**2.13**). a) LDA, THF, HMPA, -78 °C, 71%; b) DMSO, DCC, pyridinium chloride, 89%; c) DBU, DCM, r.t., then $BrCCl_3$, 0 °C, 92%; d) TBAF, THF; e) $Pd(OAc)_2$, $K_2CO_3$, MeCN, 44% over 2 steps; f) NaI, HCl, acetone, 82%.

After TBS deprotection, an intermediate quinone methide was formed and trapped by the hydroxyl group, giving natural product antipode (+)-sambutoxin (**2.13**).




**Scheme 2.5**: Synthesis of racemic 8-methylpyridoxatin (**2.14**). a) Rh-catalyst on β-75 zeolite, $H_2$, EtOH, 100 bar, 175 °C, 1 h, 82%; b) LDA, TMSCl, THF, -78 °C, 86%; c) $GaCl_3$, THF, ethynyltrimethylsilane, r.t., 5 min, 87%; d) NBS, MeCN, reflux; e) MeI, $Ag_2CO_3$, $CHCl_3$, 3 d, 42% over 2 steps; f) *n*-BuLi, THF, -78 °C; chlorooxoacetate, 1 h, 61%; g) AIBN, $Bu_3SnH$, toluene, heat, 18 h, 86%; h) MeMgI, neat, 165 °C, 2h, 72%; i) HMDS, TMSCl, reflux, 24 h; j) $MoO_5$•py•HMPA, DCM, 24 h; k) $Na_4EDTA$, $H_2O$-EtOAc, r.t., 2 h, 61% over three steps.

8-Methylpyridoxatin (**2.14**) was initially isolated as an atropisomeric mixture in 1999,[122] but the atropoisomers were later separated and the configurations assigned.[123] Reports on a possible antimalarial activity of the compounds were not conclusive, and a racemic synthesis with subsequent separation of the atropisomers has been reported by the Chai group (Scheme 2.5).[124] The synthesis started from phenol **2.33** with a hydrogenation

[122] P. Cai, D. Smith, B. Cunningham, S. Brown-Shimer, B. Katz, C. Pearce, D. Venables, D. Houck, *J. Nat. Prod*. **1999**, *62*,397.
[123] M. Isaka, M. Tanticharoen, *J. Org. Chem*. **2001**, *66*, 4803.
[124] I. L. Jones, F. K. Moore, C. L. L. Chai, *Org. Lett*., **2009**, *11*, 5526.

reaction using a zeolite supported rhodium catalyst to give a *meso*-ketone, which was then converted to the diastereomerically pure ketone **2.34**. In parallel, the 4-hydroxy pyridone **2.35** was brominated and methylated to give aryl bromide **2.36**, which was deprotonated with *n*-BuLi and quenched with ketone **2.34**, and the formed alkoxide was trapped with chlorooxoacetate to allow for a MacMillan deoxygenation.[125] Removal of the protecting groups and *N*-oxidation with Vedej's reagent[126] gave the natural product **2.14**.

In our labs we have also reported several total syntheses of pyridopolyene natural products,[127] and the next chapter details the total synthesis of (–)-pyridovericin (**2.46**).

## 2.7 Total Synthesis of (–)-Pyridovericin – a Neuritogenic Pyridone Alkaloid

### 2.7.1 Previous Synthetic Contributions

Since its isolation in 1988 by Nakagawa and co-workers,[128] pyridovericin (**2.46**) has received considerable attention from the synthetic community. In 2002, the Curran group reported a quasiracemic synthesis of both enantiomers of pyridovericin (**2.46** and **2.47**, Scheme 2.6).[129] Quasiracemic synthesis shares concepts of both racemic and enantioselective synthesis. In quasiracemic synthesis, both enantiomers are obtained in a single synthetic sequence, but like in enantioselective synthesis, the final compounds are obtained in enantioenriched form. This is achieved by initially tagging the two enantiomerically pure starting materials **2.38** and **2.42** separately at the beginning of the synthesis with two distinguishable tags and then mixing them.[130]

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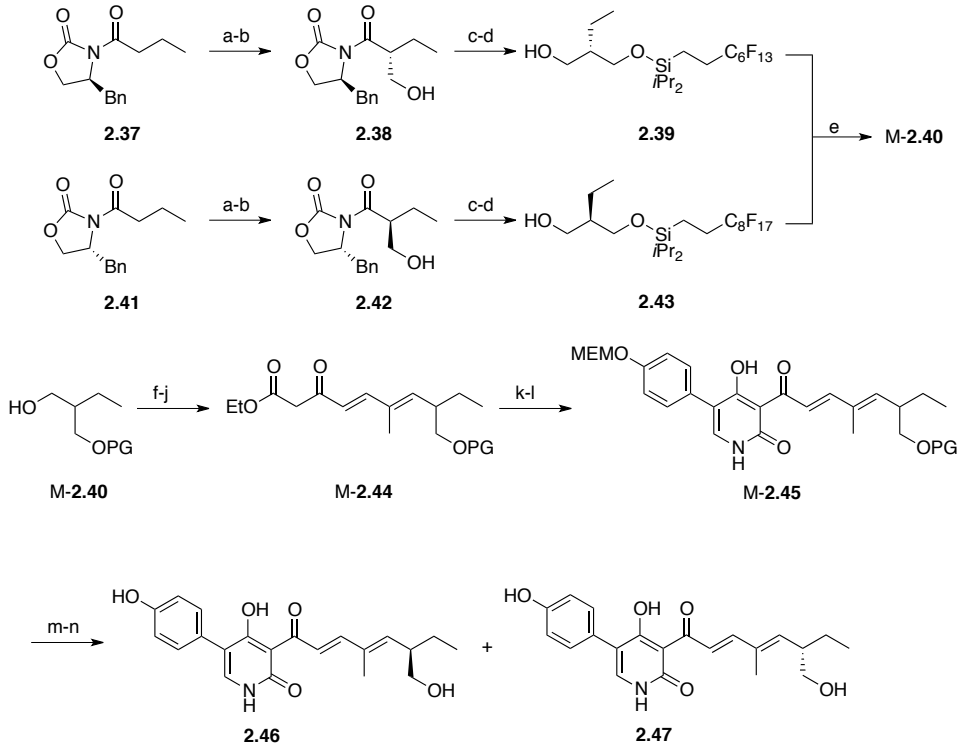
[125] S. C. Dolan, J. MacMillan, *J. Chem. Soc. Chem. Commun*.**1985**, 1588.
[126] E. Vedejs, S. Larsen, *Org. Synth*. **1987**, *64*, 127; S. A. Matlin, P. G. Sammes, *J. Chem. Soc. Chem. Commun.* **1972**, 1222.
[127] H. J. Jessen, A. Schumacher, T. Shaw, A. Pfaltz, K. Gademann, *Angew. Chem. Int. Ed.* **2011**, *50*, 4222; H. J. Jessen, A. Schumacher, F. Schmid, A. Pfaltz, K. Gademann, *Org. Lett.* **2011**, *13*, 4368; F. Schmid, M. Bernasconi, H. Jessen, A. Pfaltz, K. Gademann, *Synthesis* **2014**, *46*, 864.
[128] S. Takahashi, K. Ucha, N. Kakinuma, R. Hashimoto, T. Yanagisawa, A. Nakawaga, *J. Antibiot.* **1988**, *51*, 1051.
[129] Q. Zhang, A. Rivkin, D. P. Curran, *J. Am. Chem. Soc.* **2002**, *124*, 5774.
[130] D. P. Curran, *Angew. Chem. Int. Ed.* **1998**, *37*, 1175.

The ideal pair of tags should behave identically throughout the synthesis (e.g. reactivity, solubility, polarity, spectral characteristics, chromatography). In the end, the two tags must be able to be differentiated by at least one orthogonal reaction or separation methodology (e.g. fluourous HPLC) to separate the quasiracemic mixture and give enantiopure products.



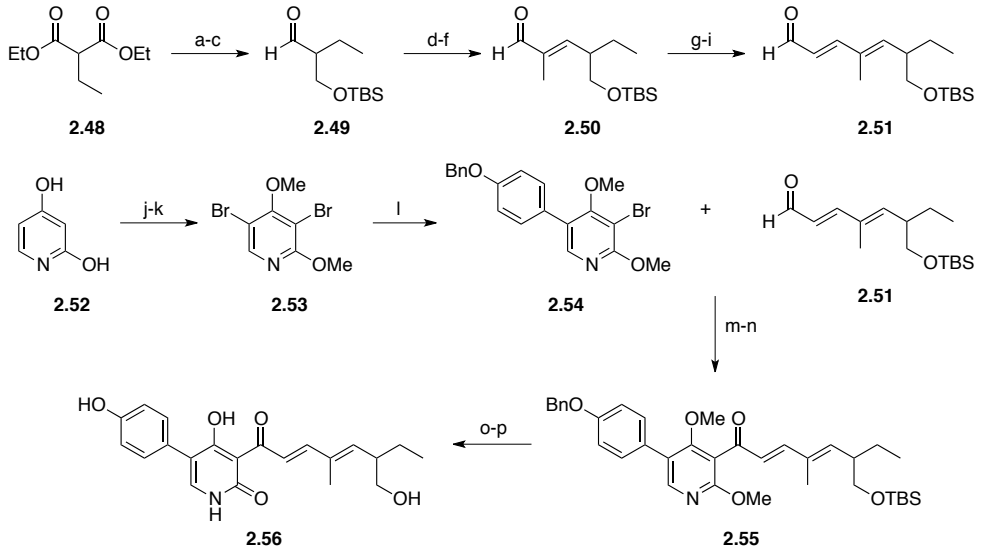

**Scheme 2.6**: Synthesis of both enantiomers of pyridovericin (**2.46** and **2.47**). a) $TiCl_4$, $NEt_3$, BOMCl, 78%; b) $H_2$, Pd/C, quant. c) $BrSi(iPr_2)CH_2CH_2C_6F_{13}$, $NEt_3$, DMAP, 89% or $BrSi(iPr_2)CH_2CH_2C_8F_{17}$, $NEt_3$, DMAP, 89% d) $LiBH_4$, 71%; e) equimolar mixing of **2.39** and **2.43**; f) $(COCl)_2$, DMSO; g) $Ph_3PC(CH_3)CO_2Et$, 73% over two steps; h) DIBAL-H; i) $(COCl)_2$, DMSO, 95% over two steps; j) $(EtO)_2P(O)CH_2C(O)CH_2CO_2Et$, LDA, 83%; k) $MEMOC_6H_4CH{=}NCO$, NaH, 58%; l) $Ph_2O$, 250 °C, 50%; m) separation by fluorous HPLC; n) TMSCl, NaI, 90%, 25% *e.e.*

In the pyridovericin synthesis of Curran, the orthogonal tags applied were two very similar silyl protecting groups with perfluorinated chains of slightly different length ($C_6F_{13}$ vs. $C_8F_{17}$).[131] These perfluorinated protecting groups were anticipated to behave similarly throughout the performed chemical transformations, but would be separable at a later stage by HPLC using a perfluorated stationary phase.[132] The synthesis of the side

[131] D. P. Curran, *Synlett* **2001**, 1488.
[132] I. T. Horváth, *Acc. Chem. Res.* **1998**, *31*, 641; D. P. Curran, *The Cancer J.* **1998**, *4* (Supp. 1), S73; L. P. Barthel-Rosa, J. A. Gladysz, *Coord. Chem. Rev.* **1999**, *192*, 587; D. P. Curran, *Pure Appl. Chem.* **2000**, *72*, 1649; D. P. Curran, Z. Y. Luo, *J. Am. Chem. Soc.* **1999**, *121*, 9069; Z. Y. Luo, J. Williams, R. W. Read, D. P. Curran, *J. Org. Chem.* **2001**, *66*, 4261.

chain started from acylated Evans auxiliary **2.37**, which was enantioselectively alkylated with BOMCl, and the benzylic group was cleaved hydrogenolytically[133] to give the two enantiomeric alcohols **2.38** and **2.42** (Scheme 2.6). These were then protected with $BrSi(iPr_2)CH_2CH_2C_6F_{13}$ or $BrSi(iPr_2)CH_2CH_2C_8F_{17}$ respectively[134] to give the quasienantiomers **2.39** and **2.43**, which where then mixed in equimolar amounts to give the quasiracemate M-**2.40**. With the quasiracemic mixture prepared, the rest of the synthesis was performed according to an adapted literature procedure. The quasiracemic alcohol M-**2.40** was oxidized to the corresponding aldehyde by Swern oxidation[135] and subjected to a Wittig reaction. After an additional reduction-oxidation-Horner-Wadsworth-Emmons (HWE) reaction sequence,[136] the quasiracemic β-keto ester M-**2.44** was obtained. The formation of the pyridone cycle M-**2.45** was then achieved by acylation of β-keto ester M-**2.44** with a vinyl isocyanate followed by thermal ring closure.[137] At this stage, the quasiracemic mixture of M-**2.45** was resolved by semi-preparative fluorous HPLC, and the obtained enantiomerically enriched pyridones were treated with TMSCl and NaI to afford the deprotected enantiomers **2.46** and **2.47** of pyridovericin. The group then applied Mosher ester $^1$H NMR analysis for the determination of the enantiomeric excess, as no chiral HPLC conditions for the separation of the racemate were found. Unfortunately, it was found that the *e.e*. had eroded from an enantiopure compound **2.39** to a low *e.e.* of 25% for **2.46** during the course of the synthesis. However, this synthetic approach still allowed for proof of concept of quasiracemic synthesis, and an example where a different enantiopure natural product is prepared with excellent *e.e. via* a quasiracemic synthesis was given in the same publication. Nevertheless, the main drawback of the synthesis was racemization of the intermediates during the sequence.

[133] M. Ihara, A. Katsumata, F. Setsu, Y. Tokunaga, K. Fukumoto, *J. Org. Chem*. **1996**, *61*, 677.
[134] B. Boutevin, F. Guida-Pietrasanta, A. Ratsimihety, G. Caporiccio, G. J. Gornowicz, *J. Fluorine Chem.* **1993**, *60*, 211.
[135] S. L. Huang, D. Swern, *J. Org. Chem*. **1978**, *43*,4537; K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651.
[136] L. Horner, H. Hoffmann, H. G. Wippel, *Chem. Ber*. **1958**, *91*, 61; L. Horner, H. Hoffman, H. G. Wippel, G. Klahre, *Chem. Ber*. **1959**, *92*, 2499; W. S. Wadsworth Jr., W. D. Emmons, *J. Am. Chem. Soc*. **1961**, *83*, 1733; W. S. Wadsworth Jr., I. O. Schupp, E. J. Sous, J. A. Ford, *J. Org. Chem*. **1965**, *30*, 680.
[137] J. H. Rigby, *Synlett* **2000**, *1*, 1.




**Scheme 2.7**: Racemic synthesis of pyridovericin (**2.56**). a) LAH, THF; b) TBSCl, NaH, THF, 60% over two steps; c) Swern oxidation; d) $Ph_3P{=}C(CH_3)CO_2Et$, toluene, 90% over two steps; e) DIBAL-H, THF f) Swern oxidation g) $Ph_3P{=}CHCO_2Et$, toluene, 78% over three steps; h) DIBAL-H, THF; i) Swern oxidation, 97% over two steps; j) $Br_2$, conc. aq. HBr; k) MeI, $Ag_2CO_3$, DCM, 45% over two steps; l) $BnOC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, $Na_2CO_3$, toluene/ethanol, 44%; m) *t*-BuLi, THF, 59%; n) $MnO_2$, DCM, 71%; o) TMSCl, NaI, MeCN, 53%; p) $BBr_3$, DCM, 75%.

The Baldwin group reported a total synthesis of racemic pyridovericin (**2.56**) in 2002.[138] The strategy was based on a two-fold functionalization of the protected dibromopyridine (**2.53**, Scheme 2.7). The synthesis of the side chain started from malonate **2.48**, which was reduced to the diol with lithium aluminum hydride, mono-TBS-protected[139] and oxidized to give aldehyde **2.49**. A Wittig-reduction-oxidation sequence gave enal **2.50**, which underwent another Wittig-reduction-oxidation sequence to give dienal **2.51**. The synthesis of the biaryl fragment **2.54** started from commercially available pyridine derivative **2.52**, which was brominated twice[140] and methylated with methyl iodide in the presence of silver carbonate.[141] The following Suzuki–Miyaura coupling[142] under conditions reported in the literature[143] proceeded in a moderate yield of 44%, as the double-arylation product and the positional isomer was also obtained in considerable amounts. The key step to couple the fragments **2.54** and **2.51** consisted of first performing a lithium-bromine exchange with *t*-BuLi and then quenching the obtained

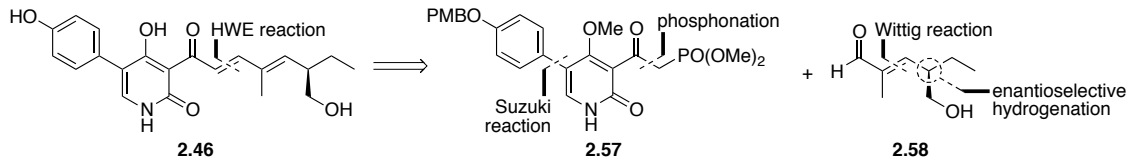
[138] J. E. Baldwin, R. M. Adlington, A. Conte, N. R. Irlapati, R. Marquez, G. J. Pritchard, *Org. Lett.* **2002**, *4*, 2125.
[139] A. B. Holmes, A. B. Hughes, A. L. Smith, *J. Chem. Soc., Perkin Trans. 1* **1993**, 633.
[140] H. J. Den Hertog, *Recl. Trav. Chim. Pays-Bas*. **1945**, *64*, 85.
[141] A. Loppinet-Serani, F. Charbonnier, C. Rolando, I. Huc, *J. Chem. Soc., Perkin Trans. 2* **1998**, 937.
[142] N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun*. **1979**, 866; N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett*. **1979**, 3437; N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun*. **1981**, *11*, 513.
[143] D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem*. **1997**, *62*, 7170.

aryllithium species with the aldehyde **2.51**. The corresponding alcohol was obtained in 59% yield, along with 20% of the quenched aryllithium species bearing an H-atom in the C(3)-position. The authors attribute this to either deprotonation of the ε-position of the aldehyde **2.51** by the aryllithium species or deprotonation of the formed *tert*-butyl bromide. The alcohol was then oxidized with activated manganese dioxide to the arylenone **2.55**, and cleavage of the methyl- and benzylic ethers with TMSCl/NaI[144] and boron tribromide,[145] respectively, gave racemic pyridovericin (**2.56**). The route involved 13 linear steps starting from the malonate **2.48** and gave the target in 7% overall yield. The established synthesis allowed the authors to further investigate the biomimetic synthesis of related natural products.[146]

Both reported syntheses relied upon a Wittig/HWE-reduction-oxidation sequence for the construction of the side chain. Curran's approach required equimolar amounts of a chiral auxiliary for the introduction of asymmetry, whereas the Baldwin group chose a racemic route. With respect to our synthesis, we found it highly desirable to apply a catalytic enantioselective transformation for introduction of the chiral element. We also would have to take special care to detect and avoid racemization observed in Curran's synthesis. The formation of the biaryl moiety was achieved in a thermal [4+2] cycloaddition in Curran's synthesis and *via* sequential functionalization of the dibromopyridine **2.53** in Baldwin's synthesis. While the latter approach was of a more modular and convergent nature, problems arose due to only moderate positional selectivity in the Suzuki reaction. Ideally, we would be able to implement two orthogonal activating groups to avoid these issues. Our retrosynthetic analysis for (–)-pyridovericin (**2.46**) is presented in the next section.

[144] K. E. Henegar, S. W. Ashford, T. A. Baughman, J. C. Sih, R. L. Gu, *J. Org. Chem.* **1997**, *62*, 6588.
[145] D. E. Ward, Y. Gai, B. F. Kaller, *J. Org. Chem*. **1995**, *60*, 7830.
[146] N. R. Irlapati, J. E. Baldwin, R. M. Adlington, G. J. Pritchard, A. Cowley, *Org. Lett.* **2003**, *5*, 2351.

### 2.7.2 Retrosynthetic Analysis




**2.46** **2.57** **2.58**

**Scheme 2.8**: Retrosynthetic analysis of (*R*)-(–)-pyridovericin **2.46** and the fragments **2.57** and **2.58**.

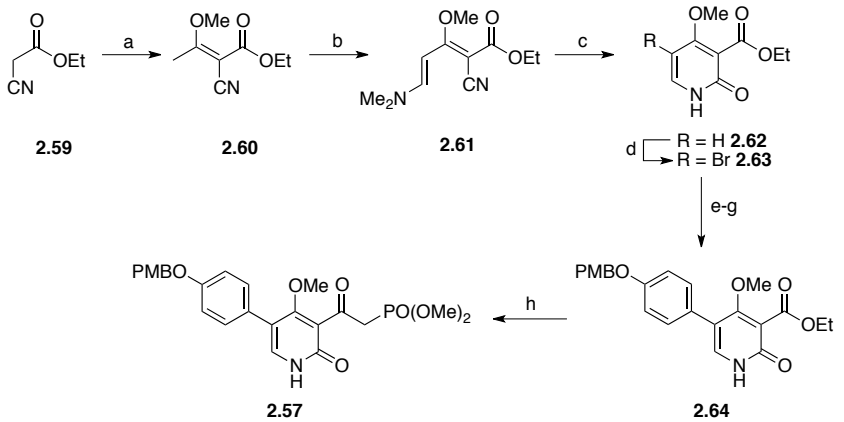
Our retrosynthetic analysis (Scheme 2.8) was based on our previously reported syntheses.[127] The building blocks **2.57** and **2.58** would be connected *via* an HWE reaction. The biaryl fragment **2.57** would be synthesized *via* a Suzuki-Miyaura coupling reaction and nucleophilic phosphonation of an ester. The enantiomerically enriched aldehyde **2.58** would be synthesized with a Wittig reaction and an enantioselective hydrogenation of a protected β-hydroxy enoate. This approach had proven to be synthetically useful before and should give high enantiomeric ratios. Judging from our previous experiences with similar targets, we should also be able to deliver the natural product in a similarly concise fashion to Baldwin's synthesis.

## 2.8 Results and Discussion

### 2.8.1 Synthesis of the Biaryl Fragment

For the synthesis of the phosphonate building block **2.57**, we relied upon a procedure developed in our group as (Scheme 2.9).[127] The synthesis of the known heterocycle **2.64**[147] started with a Knoevenagel condensation[148] between ethyl cyanoacetate **2.59** and 1,1,1-trimethoxy methane to give the enol ether **2.60**. Condensation with DMF-dimethyl acetale followed by cyclization under acidic conditions gave the pyridone **2.62**. Although the yield was rather low (25–41% over three steps), only one chromatographic purification was required in this sequence, and decagram amounts of intermediate **2.62** were readily obtainable. The yield of the subsequent electrophilic aromatic substitution with NBS to give compound **2.63** seemed to be dependent of the quality of the NBS, with freshly crystallized reagent performing best.

[147] B. Kasum, R. H. Prager, *Aust. J. Chem*. **1983**, *36*, 1455.
[148] E. Knoevenagel, *Ber*. **1894**, *27*, 2345; E. Knoevenagel, *Ber*. **1896**, *29*, 172.



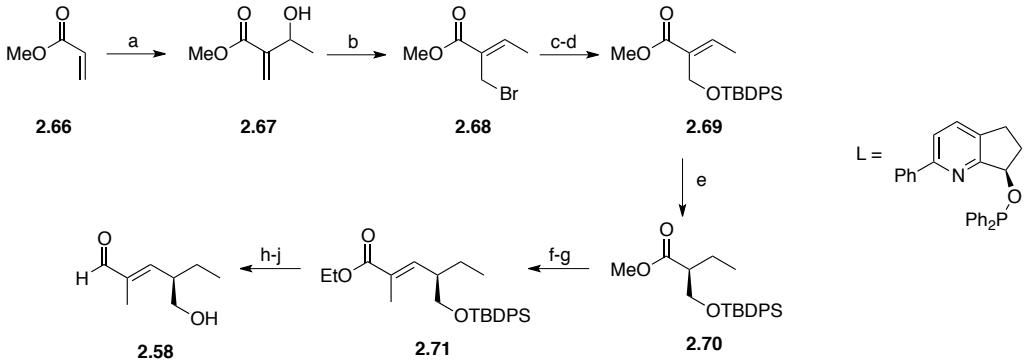

**Scheme 2.9**: Synthesis of the phosphonate **2.57**. a) $CH_3(OCH_3)_3$, reflux, 6 h; b) *N*,*N*-dimethylformamide dimethyl acetal, reflux, 2 h; c) AcOH, $H_2O$, reflux, 1 h, 25–41% over three steps; d) NBS, $NH_4NO_3$, MeCN, reflux, 45 min, 68–87%; e) SEMCl, $NEt_3$, DCM, 0 °C, 1 h, *N*-SEM 58%, *O*-SEM 42%; f) (4-[{4- methoxybenzyl}oxy]phenyl)boronic acid, $Pd(PPh_3)_4$, $K_2CO_3$, DME/$H_2O$/DMF, 60 °C; 12–24 h, quant. g) for *N*-SEM pyridone: TBAF, THF, 60 °C, 4 h, 80%; for *O*-SEM pyridine: TFA, DCM, r.t., 30 min, quant.; h) $MePO(OMe)_2$, *n*-BuLi, -78 °C, THF; **2.64**, THF, -78 °C, 93%.

The pyridone core was then SEM-protected, giving a separable mixture of *N*-SEM pyridone and *O*-SEM protected pyridine. The introduction of the protecting group was found to be necessary, as presumably the free pyridone moiety coordinates to the catalyst and deactivates it during the Suzuki-Miyaura coupling reaction. It was also found that the *O*-SEM pyridine rearranges to the *N*-SEM pyridone to a 4:5 ratio when stored at 5 °C. This could prevented by storing the compound at -20 °C. We also tried to improve the chemoselectivity of the SEM protection by introduction of silver salts in the reaction,[149] but with no success (data not shown). The Suzuki coupling reaction to introduce the PMB-protected phenol moiety gave quantitative yield, even if the regioisomeric mixture of SEM-protected compounds was applied, but thorough degassing of the solvents (freeze-pump-thaw cycle, 3x) is mandatory. Formation of black palladium precipitate indicated completion of the reaction or that reaction had stalled. The SEM groups where then removed with TBAF (for *N*-SEM derivative) or TFA in DCM (for *O*-SEM derivative) in good yields. The following formation of the phosphonate **2.57** from the ester **2.64** gave very good yields, however several parameters had to be controlled rigorously. The initial deprotonation of the dimethyl methylphosphonate had to be performed at -78 °C, and an off-white suspension indicated formation of the organolithium species. Therefore, the phosphonate solution was precooled and the *n*-BuLi solution was let run down the vessel wall in order to also

[149] M. Breugst, H. Mayr, *J. Am. Chem. Soc*. **2010**, *132*, 15380.

precool it. If no suspension was formed, the reagent proved to be insufficiently reactive for the phosphonation to occur. Furthermore, a threefold excess of reagent was required, one equivalent for the nucleophilic attack, one for the deprotonation of the pyridone and one for the deprotonation of the β-keto phosphonate. The solution of the pyridone was then also added slowly to the phosphonate suspension, as a fast addition also diminished the yield. Ideally, the rate of addition was adjusted so that the lithiated phosphonate suspension did not transform to a homogenous solution. When these requirements were met, the reaction gave reproducible yields of >90%.

### 2.8.2 Synthesis of the Side Chain




**Scheme 2.10**: Synthesis of the aldehyde **2.58**. a) Acetaldehyde, DABCO, r.t., 7 d, 80%; b) NBS, DMS, DCM, r.t., 16 h, 91%; c) NaOAc, MeOH, 80 °C, 4 h; $K_2CO_3$, MeOH, r.t., 18 h, 82%; d) TBDPSCl, Im, DCM, 0 °C to r.t., 1h, 89%; e) [Ir(L)(cod)]{B[3,5-$(CF_3)_2C_6H_3]_4$} 1 mol%, $H_2$, DCM, 0 °C, 16 h, 99%, 92:8 e.r.; f) DIBAL-H, DCM, -78 °C 1 h, 82%; g) ethyl 2- (triphenylphosphoranylidene)propanoate, DCM, reflux, 48 h, 95%; *E*/*Z* >30:1; h) DIBAL-H, THF, -78 °C to r.t., 2 h, 88%; i) TPAP, NMO, DCM, r.t., 1 h, 99%; j) TBAF, THF, r.t., 2 h, 95%.

With building block **2.57** in hand, we commenced the synthesis of aldehyde **2.58** (Scheme 2.10). The synthesis started from methacrylate **2.66**, initially following a previously reported procedure.[150] A Morita-Baylis-Hillman reaction[151] with acetaldehyde in the presence of DABCO gave the β-hydroxy ester **2.67**, which was converted under modified base-free Corey-Kim conditions[152] to give the vinyl bromide **2.68**. We only observed formation of the *E*-isomer, which was crucial for the enantioselective hydrogenation later on, as the *Z*-isomer would yield the opposite

[150] W. R. Roush, B. B. Brown, *J. Org. Chem*. **1993**, *58*, 2151.
[151] K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn*. **1968**, *41*, 2815; A. B. Baylis, M .E. D. Hillman, *Acrylic compounds*. US patent US Patent 3,743,669, **1972**, Celanese Corp.
[152] E. Vilsmaier, W. Spruegel, *Liebigs Ann. Chem*. **1971**, *747*, 151; E. J. Corey, C. U. Kim, *J. Am. Chem. Soc*. **1972**, *94*, 7586.

enantiomer.[153] Bromide **2.68** underwent substitution with sodium acetate, and the acetate intermediate was subjected to methanolysis in a one-pot procedure. The resulting allylic alcohol was TBDPS protected to give ester **2.69**. This ester was then subjected to enantioselective hydrogenation conditions developed in collaboration with the Pfaltz group. The investigations of this reaction have been extensively described elsewhere,[154] however a few key points shall be mentioned here for the sake of completeness.

The introduction of a silyl protecting group was found to be necessary, and it is proposed that for an unprotected alcohol, the hydrogenation product irreversibly binds to the catalyst, shutting down the catalytic cycle.[155] TBDPS-protected alcohol **2.69** was found to be superior to the TIPS- or TBS-protected analogs in terms of enantioselectivity. It was also observed that performing the reaction at a concentration of 0.2 M gave better selectivity than at 0.4 M. Therefore, the reaction was run in several batches on lower concentration to obtain the best enantiomeric ratios.

Ester **2.70** was obtained in good yield and e.r. and, after reduction and oxidation to the aldehyde, subjected to a Wittig reaction, which gave enoate **2.71** in excellent yield and *E*/*Z* selectivity. Attempted direct DIBAL-H reduction to the corresponding aldehyde only gave low yields, and we therefore applied a DIBAL-H reduction/Ley-Griffith oxidation[156] protocol/deprotection to furnish the aldehyde **2.58**. For the subsequent HWE-reaction, it was found necessary to remove the sterically demanding TBDPS group, as otherwise only low yields were observed.

In some cases we obtained Knoevenagel-type products such as **2.74** in the HWE reaction. We performed a screening on a test substrate **2.72** to minimize formation of this product as detailed in Table 2.1. The reactions were monitored by UPLC-MS analysis. As the absorption coefficients of the reactants were not known, this allowed only for a rough quantitative analysis. Nevertheless, this approach proved to be sufficient for optimization of the reaction.

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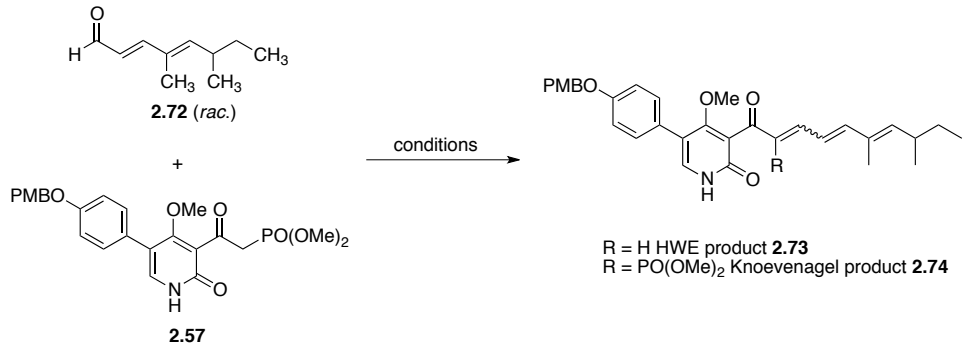
[153] A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897; S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402.
[154] A. Schumacher, *Ph.D. Thesis*; University of Basel, Switzerland, **2012**, ISBN 978–3-95404-059-9.
[155] J. Zhou, W. Oegle, Y. Fan, V. Banphavichit, Y. Zhu, K. Burgess, *Chem. Eur. J.* **2007**, *13*, 7162.
[156] A. C. Dengel, R. A. Hudson, W. P. Griffith, *Transit. Metal Chem.* **1985**, *10*, 98; W. P. Griffith, S. V. Ley , G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun*. **1987**, 1625.

**Table 2.1**: Screening of HWE conditions.



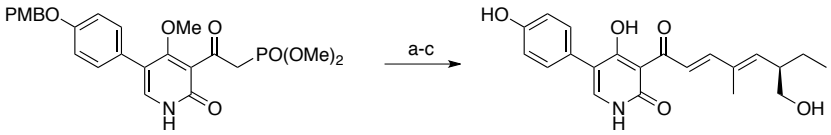

| Entry | Conditions (eq.) | Conversion (%) to 2.73 | Conversion (%) to 2.74 |
|---|---|---|---|
| 1 | DBU (1.2), THF | <50 | <50 |
| 2 | DBU (1.2), THF-$H_2O$ (4:1) | <50 | <50 |
| 3 | DBU (1.2), LiCl (2.0), THF | <50 | – |
| 4 | DBU (1.2), LiCl (2.0), THF-$H_2O$ (4:1) | >50 | – |
| 5 | LiOH (1.2), THF | <50 | traces |
| 6 | LiOH (1.2), THF-$H_2O$ (4:1) | >50 | – |

General conditions: Phosphonate **2.57** (1.0 eq.), aldehyde **2.72** (1.0 eq.), r.t. 0.2 M, exclusion of light.

We quickly noticed that the undesired product **2.74** was only formed in the absence of lithium salts (entries 1 and 2). We also observed decomposition of the product **2.74** upon adding aqueous LiOH to the reaction mixture. Lithium chloride in the presence of water proved to be beneficial for formation of the desired product **2.73** (entry 4) compared to the anhydrous conditions in entry 3. When lithium hydroxide was used as a combination of base and lithium-ion source in a THF-$H_2O$ mixture, we observed the best results in terms of product formation and side reaction suppression (entry 6). We contribute this to a solubility effect of the lithium salt as deduced from comparison with entry 5.

### 2.8.3 Coupling of the Fragments

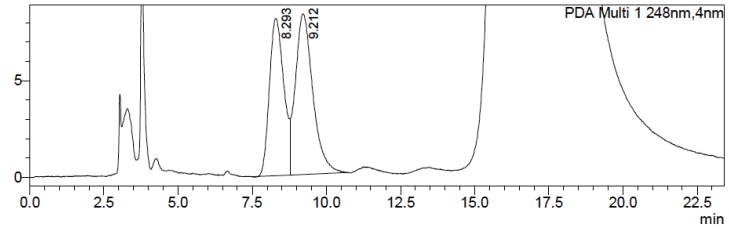
We then applied the optimized conditions to the enantiomerically enriched aldehyde **2.58** (Scheme 2.11). Although the HWE reaction required a long reaction time (6 d), we obtained the desired pyridopolyene in good yield and excellent *E*/*Z* selectivity. It should be noted that the formed pyridopolyenes are light sensitive and are prone to *E/Z* isomerization.




**2.57** **2.46**

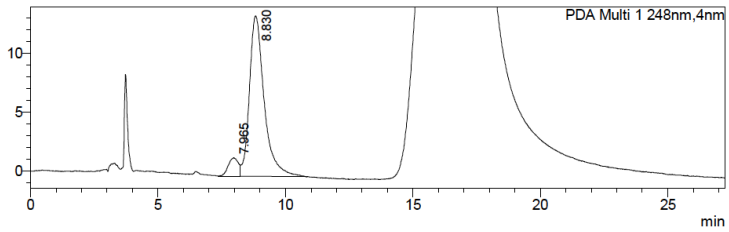
**Scheme 2.11**: Synthesis of the (–)-Pyridovericin **2.46** .a) **2.58**, LiOH, THF-$H_2O$, exclusion of light, r.t., 6 d, 77%, *E*/*Z* >30:1; b) LiI, pyridinium chloride, THF, 60 °C, 4 h; c) TFA, DCM, r.t., 30 min, 83% over to steps, 93:7 e.r., *E*/*Z* >6:1, *E*/*Z* >30:1 after recrystallization.

The reactions were therefore carried out under exclusion of light, and light exposure was also minimized during workup and storage. After removal of the protecting groups we obtained (–)-pyridovericin (**2.46**) in good yield and in a moderate *E*/*Z* ratio of about 6:1 after flash chromatography. However, we were able to increase this ratio to >30:1 upon repeated fractional crystallization. The e.r. was determined to be 93:7 by comparison of chiral HPLC traces with the racemic compound (Figure 2.8).




PDA Ch1 248nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 8.293 | 8130 | 273480 | 44.484 |
| 2 | 9.212 | 8294 | 341303 | 55.516 |
| Total | | 16423 | 614784 | 100.000 |




PDA Ch1 248nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 7.965 | 1558 | 43474 | 7.325 |
| 2 | 8.830 | 13644 | 550052 | 92.675 |
| Total | | 15202 | 593527 | 100.000 |

**Figure 2.8**: Chiral HPLC trace of the racemic compound (up) and (–)-pyridovericin (below).

In summary, the natural *R*-(–)-isomer of pyridovericin (**2.46**) was synthesized in 13 linear steps and in 22% yield from methyl acrylate (**2.66**). The key steps involved the enantioselective hydrogenation of TBDPS-protected enoate **2.69** and the coupling of phosphonate fragment **2.57** to the aldehyde **2.58**. In comparison to the other reported syntheses of pyridovericin (section 2.71), we could successfully avoid racemization during the route, as proven by analysis of chiral HPLC traces of several intermediates (see SI).

## 2.9 Pyridopolyene Natural Products as Light-Triggered Molecular Switches

As already discussed in section 2.4, pyridone natural products have been shown to possess neuritogenic activity, and we have confirmed these results independently with our synthetic material of several natural products.[127] As mentioned in the previous section, the polyene side chains of these pyridopolyenes were found to be configurationally labile, and *E*/*Z* isomerization was observed when the samples were exposed to ambient and UV light. While the rate of isomerization under ambient light was found to be slow, care had to be taken when samples were exposed to UV irradiation (*e.g.* UV detection in semi-preparative HPLC), as mixtures of *E/Z*-isomers were obtained within minutes.

**Figure 2.9**: *Ophiocordyceps* growing from a dead ant attached to a leaf.[157]

Enthomopathogenic fungi have been shown to induce behavioral changes in the host organism (see section 2.4). *Ophiocordyceps unilateralis* for example was found to cause host ants to leave their hive and let them seek areas with suitable humidity and temperature for fungal growth, where the fungal infection then would cause the ant to irreversibly attach to the major vein on the underside of leaves (Figure 2.9). The infected ant would now remain attached to the leaf until death, while the fruiting body would begin to protrude from the host and distribute spores from the newly gained vantage point (classical summit disease, section 2.4).[158]

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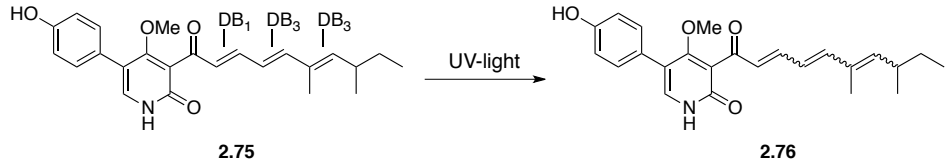
[157] M. B. Pontoppidan, W. Himaman, N. L. Hywel-Jones, J. J. Boomsma, D. P. Hughes, *PLoS ONE* **2009**, *4*, e4835; used under permission of creative commons license CC-BY 2.5.
[158] S. Mongkolsamrit, N. Kobmoo, K. Tasanathai, A. Khonsanit, W. Noisripoom, P. Srikitikulchai, R. Somnuk, J. J. Luangsa-ard, *J. Inv. Pat.* **2012**, *111*, 217.




**2.75** **2.76**

**Scheme 2.12**: Isomerization of the model substrate **2.75** upon UV irradiation.

We therefore hypothesized that the polyene side chain could function as a molecular switch, whereupon light exposure and conformational change a biological response might be triggered, as it has been shown for some host insects.[159] We decided to further investigate the isomerization behavior of these pyridopolyene natural products on the model substrate **2.75** (Scheme 2.12).

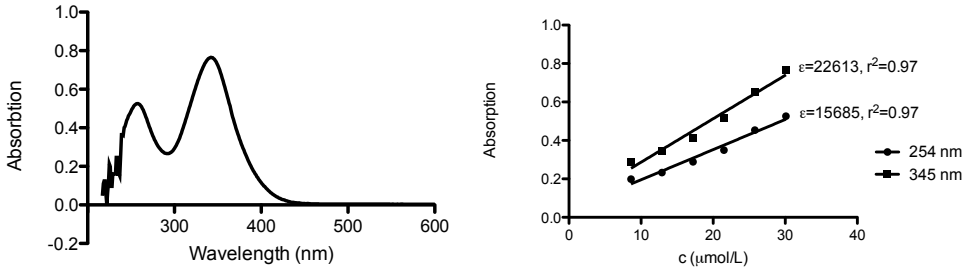



**Figure 2.10**: UV-Vis spectrum (left) and determination of ε (right) of **2.75**.

We began our studies by recording UV-Vis spectra, identifying the absorption maxima and calculating the corresponding molar absorption coefficients ε (Figure 2.10). The absorption maxima $\lambda_{max}$ were detected at 254 nm and 345 nm, with the corresponding molar absorption coefficients of 15685 $M^{-1}cm^{-1}$ and 22613 $M^{-1}cm^{-1}$ respectively. In order to further characterize the spectroscopic properties of model substrate **2.75**, we measured emission spectra of the identified $\lambda_{max}$. The sample was irradiated with a constant wavelength of 260 nm or 345 nm and the corresponding emission spectra were recorded (Figure 2.10). Compound **2.75** exhibited an emission at 481 nm when irradiated at 260 nm, and another emission maximum at 575 nm when irradiated at 345 nm, which matched well with the observed yellow-orange color of the pyridopolyene natural products.

[159] R. J. Milner, D. G. Holdom, T. R. Glare, *Entomol. Exp. Appl*. **1984**, *36*, 37; T. Ohbayashi, K. Iwabuchi, *Appl. Entomol. Zool*. **1991**, *26*, 479.

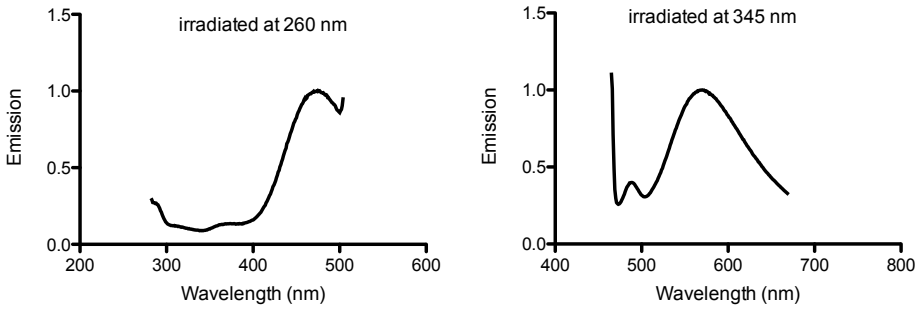



**Figure 2.11**: Emission spectra of **2.75** at 260 nm (left) and 345 nm (right).

We then designed an experiment to quantify the rate and extent of *E/Z* isomerization. A solution of **2.75** in deuterated chloroform in a $^1$H NMR tube was irradiated at 366 nm and the $^1$H NMR spectra were recorded at several intervals, monitoring the isomerization. The initial *E/Z* ratios for the three double bonds $DB_1$, $DB_2$ and $DB_3$ were determined to be 19:1, 20:1 and 17:1 respectively (Scheme 2.12, left). The obtained data is represented in an *E/Z* vs. time plot (Figure 2.11, right) and an overlay of the change in $^1$H NMR spectra over time (Figure 2.11, left).

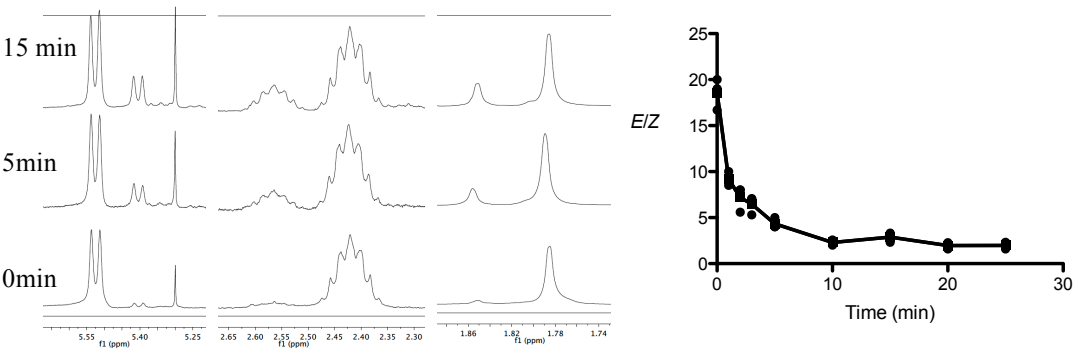


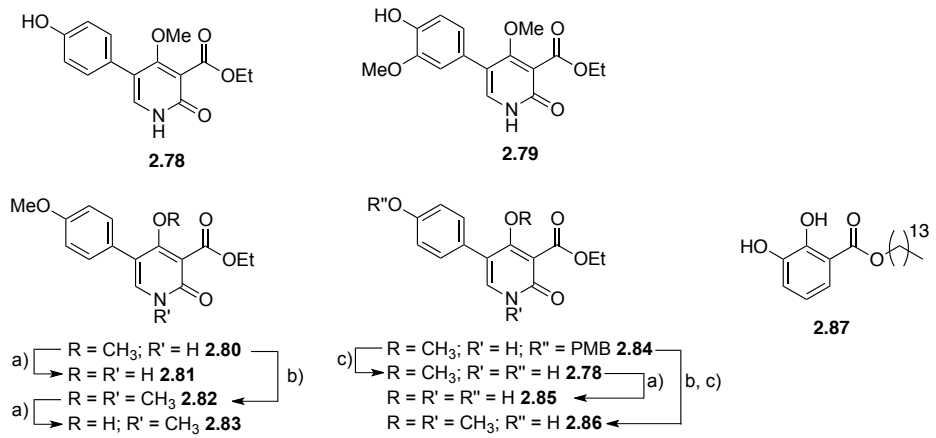

**Figure 2.12**: Selected $^1$H NMR signals of **2.75** at different times (left) and development of *E/Z* ratio with time (right).

The compounds underwent isomerization to an *E/Z* ratio of about 2:1 within ten minutes for all double bonds $DB_1$, $DB_2$ and $DB_3$. During our syntheses of pyridopolyene natural products, we mainly observed the isomerization of $DB_3$, but we were not able to identify any preferential site of isomerization in our UV-NMR experiments. Although these findings did not disprove our hypothesis of the polyene side chain acting as a molecular switch, we found the compounds proved to be challenging to handle, as for example the starting *E/Z* ratios varied from batch to batch (17:1 to 24:1). This would have rendered prospect bioassays difficult to reproduce. Our further investigations involving truncation of pyridopolyene natural products and their application in a bioactive surface material are presented in the next section.

## 2.10 Truncated Pyridone Natural Products in a Neuritogenic Functional Material

As described in section 2.3, the truncation of natural products is a powerful method for the generation of biologically active structural analogs while decreasing molecular- and synthetic complexity. Our group had already demonstrated the successful implementation of biologically active natural product-related compounds into functional surfaces and materials.[160] Therefore, we initiated a two-phase project consisting of the truncation and identification of the neuritogenic core structure of the pyridopolyene natural products, and, in a secondary stage, the application of the truncated compound in a biologically active functional material.

### 2.10.1 Truncation of Neuritogenic Pyridopolyene Natural Products




**Scheme 2.13**: Neuritogenic truncated analogs **2.78** and **2.79** and synthesis of methylated derivatives **2.80**-**2.86**. a) LiI, THF, reflux; b) MeI, $K_2CO_3$, MeCN; c) TFA (5% in DCM), r.t., 30 min.

The synthesis and identification of the neuritogenic core structures has been extensively described elsewhere.[161] The major conclusions of these investigations are summarized in this section. As described in section 2.72, our synthetic approach allowed for easy variation of the aryl substituent by Suzuki coupling. Using this approach, we synthesized a small library and identified the hydroxy substituted compounds **2.78** and **2.79** as the most active in the PC-12 assay.

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[160] J.-Y. Wach, S. Bonazzi, K. Gademann, *Angew. Chem. Int. Ed.* **2008**, *47*, 7123; R. Wehlauch, J. Hoecker, K. Gademann, *ChemPlusChem* **2012**, *77*, 1071; J. Gomes, A. Grunau, A. K. Lawrence, L. Eberl, K. Gademann, *Chimia* **2013**, *67*, 275.
[161] F. Schmid, H. J. Jessen, P. Burch, K. Gademann, *Med. Chem. Commun.* **2012**, *4*, 135.

The polyene side chain was found to be unrequired for the induction of neurite outgrowth. Thereby, we had already achieved a major simplification of the biologically active structure. We then tried to further elucidate the role of the three H-bond donor- and acceptor substituents for biological activity and synthesized all combinations of methylated derivatives to block the specific positions (compounds **2.80**-**2.86**, Scheme 2.13).

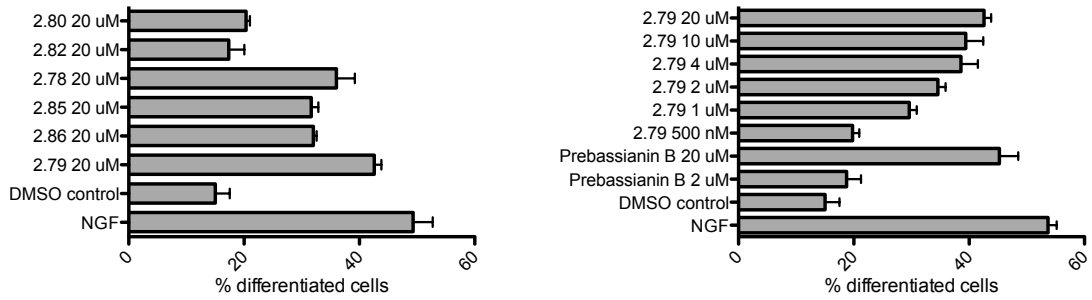


**Figure 2.13**: Screening of H-bond substituents (left) and dilution series of **2.79** (right). Errors are indicated as standard error of the mean.

We then evaluated the neuritogenic activity of compounds **2.80**-**2.86** in the PC-12 assay.[162] The summarized results of the study are presented in Figure 2.13. The 4'-methoxy substituted analogs **2.80** and **2.82** did not induce neurite outgrowth at 20 μM, whereas compounds **2.84**-**2.86** and **2.78** were all active at this concentration (Figure 2.13, left). This indicated the necessity of a 4'-hydroxy substituent for neuritogenic activity, whereas blocking the 1- and 4-positions with a methyl group did not reduce neuritogenic activity (compounds **2.80**-**2.83**). We also identified compound **2.79** as the most active of our library, with neuritogenic activity observed at a minimal concentration of 1 μM, whereas the natural product prebassianin B did not display any activity at this concentration (Figure 2.13, right).

Through these studies we have been truncate the neuritogenic core structure of the pyridopolyene natural products and even identifying a more active analog **2.79**. This was only possible due to our modular synthetic approach, which allowed for the synthesis of described analogs in scales useful for application in a bioactive functional material as described in the next section.

[162] Cell culture experiments were performed by Dr. Henning Jessen and Dr. Patrick Burch.

### 2.10.2 Neuritogenic Surfaces Using Truncated Natural Product Analogs

With the truncated and highly neuritogenic compound **2.79** in hand, we sought out to implement it in a biocompatible material, giving access to a neuritogenic surface material. The summary of our detailed study[163] is presented in this section.

Our group had extensive knowledge of the preparation and functionalization of biologically active surfaces.[160] Since the introduction of an anchoring group often elongates the synthetic sequence, we intended to incorporate compounds such as **2.78** or **2.79** directly into the functional surface without further synthetic modification. The method should also be compatible with the setup of the PC-12 assay. Although the assay was usually performed in commercial pre-coated collagen 24-well plates, such plates can readily be coated with various polymer supports.[164] We therefore sought to find a suitable method for adding our truncated neuritogenic compound **2.79** to the standard collagen coating procedures described in the literature. The general experimental setup is depicted in Figure 2.14. The process involved coating of the glass cover slides with the standard collagen solution (Figure 2.14 right, labeled blank in graphs below) and a collagen solution with a neuritogenic additive (Figure 2.14, left). After thorough rinsing, the coated glass slides were subjected to our standard PC-12 assay procedure in 24-well plates. After two days, the cells were fixed, stained and micrographs were recorded and statistically evaluated in order to assess neuritogenic activity.[165] The main parameters to be optimized were the coating temperature and time, and the concentration and solvent of the neuritogenic compound solution applied in the coating process. We decided to perform the seminal studies with the highly neuritogenic model compound tetradecyl 2,3-dihydroxybenzoate (**2.87**, Scheme 2.13).[166]

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[163] P. Burch, F. Schmid, K. Gademann, *Adv. Healthc. Mater.* **2014**, *3*, 1415.
[164] M. Buttiglione, F. Vitiello, E. Sardella, L. Petrone, M. Nardulli, P. Favia, R. d'Agostino, R. Gristina, *Biomaterials* **2007**, *28*, 2932.
[165] Cell experiments were performed by Dr. Patrick Burch. Further details are avaialble in "*Synthesis, Biological Evaluation and Surface Applications of Neuritogenic Compounds*", Patrick Burch, PhD Thesis, **2014**, University of Basel.
[166] L. Gao, J. Li, J. Qi, *Bioorg. Med. Chem.* **2010**, *18*, 2131; L. Gao, L. Xiang, Y. Luo, G. Wang, J. Li, J. Qi, Bioorg. *Med. Chem.* **2010**, *18*, 6995; Y. Luo, K. Sun, L. Li, L. Gao, G. Wang, Y. Qu, L. Xiang, L. Chen, Y. Hu, J. Qi, *ChemMedChem* **2011**, *6*, 1986.

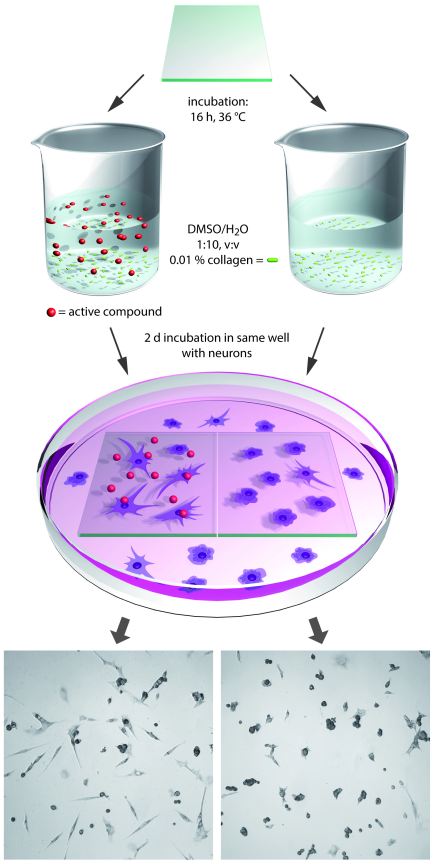


**Figure 2.14**: Experimental setup of the surface coating experiments for the generation of neuritogenic surfaces.

We identified a concentration range from 1 mM to 100 nM to significantly induce neurite outgrowth (Figure 2.15, left). Further experiments were then conducted with a 1 µM coating solution (10 µM stock solution diluted 1:10 *v/v*), and we observed increased detachment of the cells from the surface for higher concentrations. In parallel, we performed a screening of the optimal coating temperature and time and found that a coating time of 16 h at 36 °C gave the highest rate of differentiated cells (Figure 2.15, right).

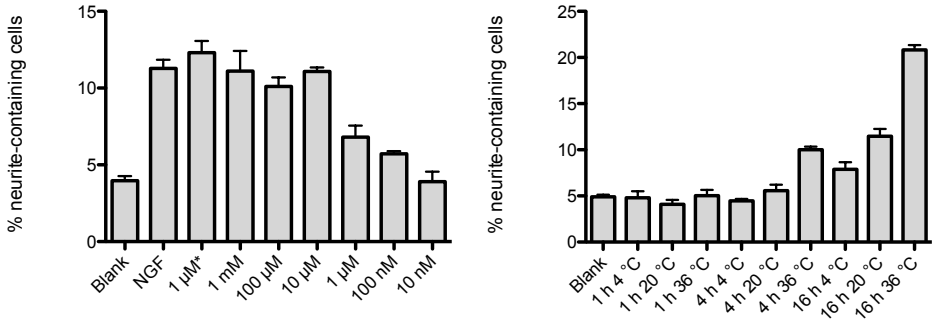


**Figure 2.15**: Screening of concentrations (left) and coating conditions (right). Errors are indicated as standard error of the mean. *Compound positive control: Surfaces coated without the active compound **2.87**, and **2.87** was subsequently added to the growth medium as DMSO solution to give a final concentration of 1 µM.

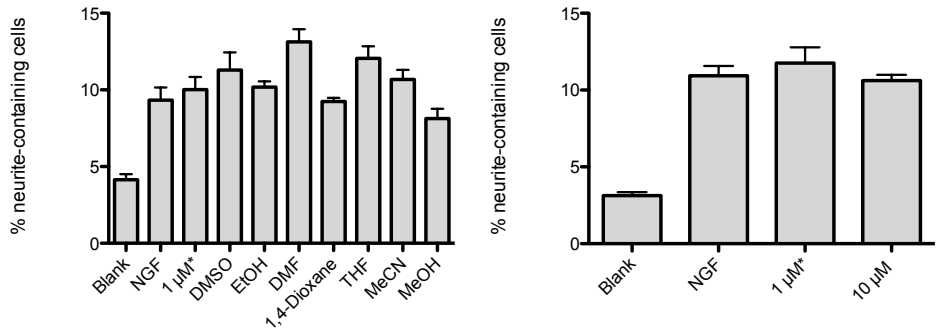


**Figure 2.16**: Screening of solvents (left) and co-incubation experiments (right). Errors are indicated as standard error of the mean. *Compound positive control: Surfaces coated without the active compound **2.87**, and **2.87** was subsequently added to the growth medium as DMSO solution to give a final concentration of 1 μM.

We then investigated the influence of the solvent of the stock solution in the coating process (Figure 2.16, left). We obtained positive results for all water-miscible solvents that were tested and prepared further stock solutions in DMSO, as it is available in sterile cell culture grade and widely applied in cell culture experiments. We then tried to gain further insight into the mechanism of neurite growth induction. Usually, control blank experiments with collagen-coated glass slides without a neuritogenic additive were performed in separate wells of the 24 well plate. Leeching of the neuritogenic compounds from the collagen surface into the medium could be a possible mechanism of distribution of the compound. Therefore, we performed co-incubation experiments with the blank glass slides and the slides coated with the neuritogenic compound in the same well on a six well plate (Figure 2.16, right). We were not able to detect increased neuron differentiation on the blank slides placed adjacent to the neuritogenic coated slides, and UPLC analysis gave no indication of the compound **2.87** being present in the cell medium within the limits of detection (1 μM). We then tested whether the coated slides would retain their neuritogenic properties throughout several cycles of cell incubation (Figure 2.17, left). After the first cycle of cell incubation (2 d), the cells were detached from the glass slides using trypsin solution, the slides were washed and sterilized and subjected to another cycle of incubation (2 d) with new cells. Although a significant induction of neurite outgrowth was still observable after three cycles, the activity of the slides had clearly decreased.

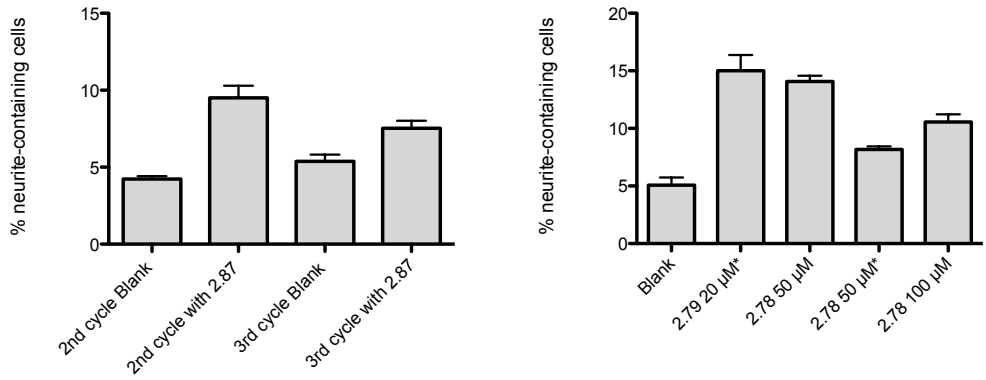


**Figure 2.17**: Screening of truncated natural products (left) and recycling of the covered slides experiments (right). Errors are indicated as standard error of the mean. *Compound positive control: Surfaces coated without the indicated active compound, and the indicated active compound was subsequently added to the growth medium as a DMSO solution to give the final concentration indicated.

Finally, we concluded the project by the application of the truncated natural product analogs **2.78** and **2.79** in the surface material (Figure 2.17, right). Although we had to raise the concentration of neuritogenic compound in the coating solution, we observed significant induction of neurite outgrowth. We were also able to even further broaden the scope of the developed methodology by replacing collagen by polylysine, another widely applied coating material in cell biology experiments, in the coating solution (data not shown).

In summary, we have successfully truncated the pyridopolyene natural products and identified the neuritogenic core. We were then able to integrate the truncated analog into a newly developed neuritogenic functional material with a robust and general approach.

## 2.11 Conclusion and Outlook

We were able to enantioselectively synthesize the pyridopolyene natural product (–)-pyridovericin (**2.46**) based upon our previously developed modular and convergent approach in good yield and enantiomeric ratio.

Our biological investigations of the pyridopolyene natural products commenced with the study of the light-triggered *E/Z* isomerization of model substrate **2.75** by UV-Vis, fluorescence and $^{1}$H NMR spectroscopy. Measuring the degree of neuron differentiation in the PC-12 assay, we then continued with the identification of the neuritogenic core and truncation of the natural products. This was accomplished by varying the aryl substituent in the C(4) position by Suzuki coupling and selectively blocking hydrogen bonding sites by methylation, which eventually yielded neuritogenic truncated analogs

**2.78** and **2.79**. These analogs were more easily accessed and showed higher neuritogenic activity as compared to the natural products. Our final project involved incorporation of the truncated analogs **2.78** and **2.79** onto a neuritogenic surface material. By adaption of a standard collagen coating protocol for cell assays, we had optimized coating concentrations, temperatures and times, and identified suitable solvents and other coating matrices than collagen.

Looking forward, the pyridopolyene natural products surely hold more undiscovered potential, especially from a biological point of view. While our research has mainly been focused on the neuritogenic properties of these compounds, we are and other groups are also investigating other biological targets.[167] In the next chapter, we will further dwell into the synthesis of another family of natural products, the aetheramides.

[167] M. de Souza Santos, W. J. Andrioli, M. P. F. de Morais Del Lama, J. K. Bastos, N. P. D. Nanayakkara, R. M. Z. G. Naal, *International Immunopharmacology,* **2013**, 1.

# 3 SYNTHETIC STUDIES TOWARDS AETHERAMIDE B

## 3.1 HIV and AIDS

The human immunodeficiency virus (HIV) is the cause of an accumulation of medical conditions summarized under the term acquired immunodeficiency disease syndrome (AIDS). The HI virus is the result of several cross-species virus transmissions and originates from simian immunodeficiency viruses (SIV) found in African primates such as macaques or chimpanzees.[168] Phylogenetic and statistical analyses date the last common ancestor and modern HIV-1 with other virus sub-types between 1910 and 1930,[169] therefore taking between 50 to 70 years before being recognized as an individual disease in 1981.[170] This delay of onset of the pandemic is explained by the fact that although infections in sub-Saharan Africa have occurred before the major global outbreak in the 1980s, the infected individuals (e.g. hunters and farmers) lived in secluded areas preventing further spreading of the disease. Shortly after identifying AIDS as a disease, the causative agent was found to be the HI virus.[171] The main transmission pathways were identified to be *via* sexual transmission, percutaneous transmission (*e.g.* reuse of hypodermic needles by recreational drug addicts) and perinatal transmission, although sexual transmission is the major pathway for infection.[172] As of 2008, the lowest estimations state the minimal number of infected individuals to be at least 60 million, with a 25 million death toll.[173] Since the main group of infected individuals consists of young adults in developing countries, the available palliative treatments are often prohibitively expensive. The applied strategies and available treatments are discussed in the next section.

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[168] P. M. Sharp, B. H. Hahn, *Cold Spring Harbor Perspectives in Medicine* **2011**, *1*, a006841.
[169] M. Worobey, M. L. Santiago, B. F. Keele, J. B. Ndjango, J. B. Joy, B. L. Labama, A. B. Dhed, G. M. Saw, *Nature*, **2004**, *428*, 820.
[170] F. P. Siegal, C. Lopez, G. S. Hammer, A. E. Brown, S. J. Kornfeld. J. Gold, S. Z, Hirschman, C. Cunningham-Rundles, B. R. Adelsberg, *N. Engl. J. Med.* **1981**, *305*, 1439; M. S. Gottlieb, R. Schroff, H. M. Schanker, J. D. Weisman, P. T. Fan, R. A. Wolf, A. Saxon, *N. Engl. J. Med.* **1981**, *305*, 1425.
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[173] M. H. Merson, J. O'Malley, D. Serwadda, C. Apisuk, *Lancet* **2008**, *372*, 475.

## 3.2 Current Treatments of HIV Infection and AIDS

In order to understand the available treatment methods, the underlying cellular mechanisms of HIV infection are briefly outlined in the following paragraph. The HI virus is a retrovirus, therefore relying on replication of its single stranded RNA by reverse transcription in the host cell as an obligatory parasite.[174] The virus effectively "hijacks" parts of the cellular machinery in order to replicate, killing the host cell in the process. HIV targets human immune cells (e.g. T helper cells or macrophages),[175] and this results in a decrease of available immune responses of the human body leading to AIDS, where an otherwise moderately severe condition (e.g. pneumonia) can cause death. The key steps of the viral reproduction cycle are highlighted in Figure 3.1.

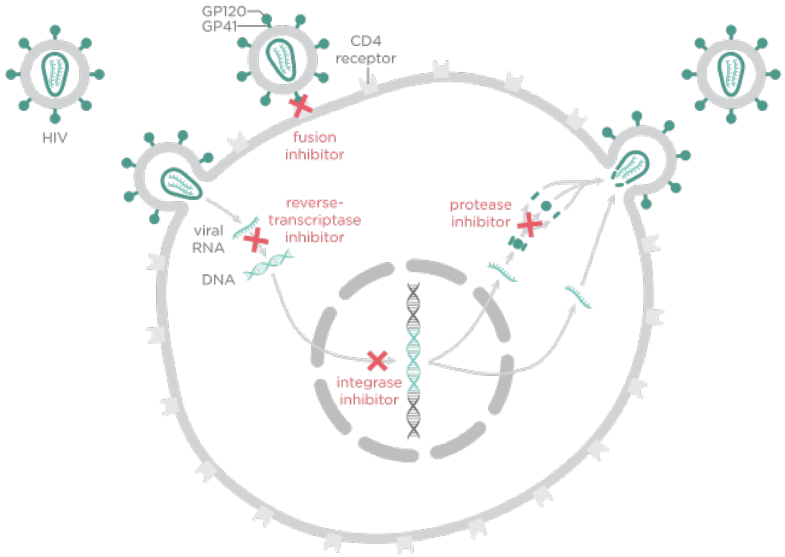


**Figure 3.1**: Key steps of HIV reproduction cycle and points of medical intervention.[176]

The first class of medication are reverse-transcriptase inhibitors. These compounds incorporate an unnatural nucleotide or -nucleoside into the newly formed DNA strain in the reverse transcriptase step, where viral RNA is translated to DNA.

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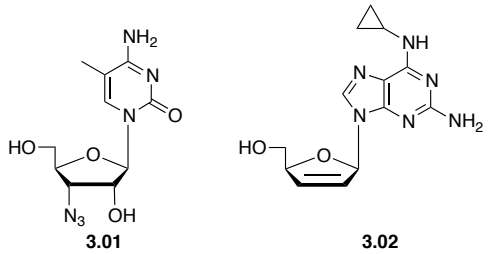
[174] R. Sanchez-Pescador, M. D. Power, P. J. Barr, K. S. Steimer, M. M. Stempien, S. L. Brown-Shimer, W. W. Gee, A. Renard, A. Randolph, J. A. Levy, *Science* **1985**, *227*, 484; L. Ratner, W. Haseltine, R. Patarca, K. J. Livak, B. Starcich, S. F. Josephs, E. R. Doran, J. A. Rafalski, E. A. Whitehorn, K. Baumeister, *Nature* **1985**, *313*, 277; S. Wain-Hobson, P. Sonigo, O. Danos, S. Cole, M. Alizon, *Cell* **1985**, *40*, 9.

[175] M. E. Harper, L. M. Marselle, R. C. Gallo, F. Wong-Staal, *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 772. G. M. Shaw, B. H. Hahn, S. K. Arya, J. E. Groopman, R.C. Gallo, F. Wong-Staal, *Science* **1984**, *226*, 1165.

[176] http://commons.wikimedia.org/wiki/File:HIV-drug-classes.svg#metadata, Thomas Splettstoesser, www.scistyle.com, Creative Commons license CC-BY-SA 3.0.

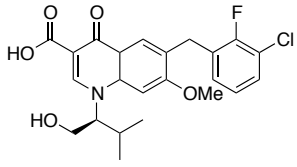
This then terminates the DNA chain elongation, and the incomplete DNA chain is not able to induce viral peptide expression (*vide infra*). Examples of such compounds are Zidovudine (**3.01**) and Abacavir (**3.02**) (Figure 3.2).[177]




**3.01** **3.02**

**Figure 3.2**: The nucleotide transcriptase inhibitors Zidovudine (3.01) and Abacavir (3.02).

Once the viral RNA is translated, the resulting viral DNA must be introduced to the hosts DNA in order to be translated into viral proteins. HIV integrase is the enzyme responsible for the incorporation of the transcripted viral DNA into the host cells DNA in the nucleus. A compound that is able to interfere at this stage of the viral reproduction cycle is Elvitegravir (**3.03**, Figure 3.3), which binds to the viral integrase enzymes, therefore inhibiting integration of viral DNA into the host cells' DNA.[178]

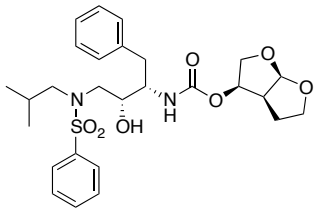



**3.03**

**Figure 3.3**: The integrase inhibitor Elvitegravir (**3.03**).

After the translated viral DNA has been successfully merged with the host DNA in the nucleus by the integrase enzyme, the host cell will start with the translation of the newly introduced viral DNA into proteins. The resulting viral polypeptide chain is cleaved at the appropriate sequences to give viral enzymes. HIV achieves this process by the use of protease enzymes. Protease inhibitors inhibit the cleavage of the translated polypeptide chain and therefore decrease viral enzyme accumulation in the host cell. Darunavir (**3.04**, Figure 3.4), developed by the group of Arun K. Ghosh, is currently the recommended first line protease inhibitor.[179]

[177] K. Wright, *Nature* **1986**, *323*, 283.
[178] K. Shimura, E. Kodama, Y. Sakagami, *J. Virol.* **2007**, *82*, 764.
[179] A. K. Ghosh, Z. L. Dawson, H. Mitsuya, *Bioorg. Med. Chem.* **2007**, *15*, 7576.



**3.04**

**Figure 3.4**: The protease inhibitor Darunavir (**3.04**).

While all the agents described above target processes inside the host cell, there are also compounds that block the initial entrance of viral RNA into the host. This class of compounds is called fusion inhibitors, and Enfurvirtide is an example of a polypeptidic medication of this class with the peptide sequence: Ac-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-$NH_2$.[180]

While all these therapeutics are effective to a certain extent, they are usually applied in a combined approach where at least two different stages of viral reproduction are targeted. This approach is known as highly active antiretroviral therapy (HAART). Since HIV has a rather fast reproduction cycle of 1.5 days from cell entrance to release of new virions and infection of other cells, it is prone to develop drug- and multidrug resistant mutants, which is less likely when HAART is applied.[181] With the currently available treatments, it is possible to render HIV infection a chronic disease with life-long treatment and without development of AIDS, whereas no treatment usually leads to death of the patient within 9 to 11 years.[182] It is, however, not yet possible to completely cure HIV infection or AIDS, although of course new medications and vaccine approaches are under investigation.[183] The "*evolutionary wisdom enshrined in natural products*"[184] might help to further clarify the cellular mechanisms and biochemical aspects of HIV and AIDS and might even pave the way to new forms of treatment.[185]

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[180] J. P. Lalezari, J. J. Eron, M. Carlson, C. Cohen, E. Dejesus, R. C. Arduino, J. E. Gallant, P. Volberding, *AIDS (London, England)* **2007**, *17*, 691.
[181] J. T. King, A. C. Justice, M. S. Roberts, C. C. Chang, J. S. Fusco, *Med. Decis. Making* **2003**, *23*, 9; C. M. Kitchen, S. G. Kitchen, J. A. Dubin, M. S. Gottieb, *Clin. Infect. Dis*. **2001**, *33*, 466; W. M. Valenti, *AIDS Reader*, **2001**, *11*, 260.
[182] S. D. Geeks, S. R. Lewin, D. V. Havlir, *The Lancet* **2013**, *382*, 1525.
[183] G. Kumari, R. K. Singh, *HIV & AIDS Review* **2012**, *11*, 5.
[184] K. Gademann, *CHIMIA* **2006**, *60*, 841.
[185] X. Ma, L. Li, T. Zhu, M. Ba, G. Li, Q. Gu, Y. Guo, D. Li, *J. Nat. Prod.* **2013**, *76*, 2298; H. R. Bokesch, A. Wamiru, S. F. J. Le Grice, J. A. Beutler, T. C. McKee, J. B. McMahon, *J. Nat. Prod.* **2008**, *71*, 1634.

## 3.3 Depsipeptides – a Class of Non-Ribosomal Peptides

### 3.3.1 The Biosynthesis of Depsipeptides

A polypeptide where one of the amide bonds is replaced by an ester bond is called a depsipeptide (Figure 3.5).

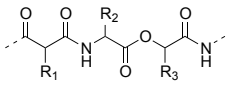

**Figure 3.5**: Characteristic structural motif of depsipeptides.

Depsipeptides are non-ribosomal peptides (NRP), which means they are not synthesized in the ribosome and, therefore, do not require an mRNA template for biosynthesis.[186] Therefore, each NRP synthetase complex can only synthesize one specific peptide. NRP are produced by microorganisms such as bacteria or fungi and, although NRP have been found in higher organisms (e.g. nudibranchs), it is believed that these were isolated from microorganisms living with the investigated specimen.[187] The biosynthetic machinery of NRP synthesis (NRPS) consists of several modules, with each module containing distinct domains. Figure 3.6 illustrates the general biosynthetic pathway of NRPS.

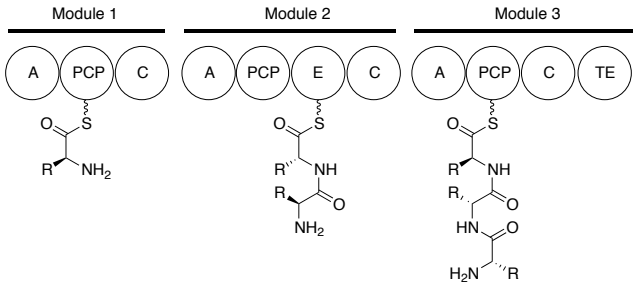


**Figure 3.6**: General NRPS pathway.

As mentioned before, the biosynthetic pathway can be divided into several modules, in this example modules 1 to 3. Each NRPS module contains at least three domains. The adenylation domain (A) is responsible for substrate recognition and initial activation.[188] The activated substrate is then transferred to the peptide carrier protein domain (PCP), which is the transport unit shuttling the carried protein to the catalytic sites of the

[186] N. J. Hansen, *Annu. Rev. Microbiol*. **1993**, *47*, 53; H. –G. Sahl, R. W. Jack, G. Bierbaum, *Eur. J. Biochem*. **1995**, *230*, 827; L. C. Vining, *Annu. Rev. Microbiol*. **1990**, *44*, 395.
[187] F. Tiburzi, P. Visca, F. Imperi, *TBMB* **2007**, *59*, 730.
[188] R. Dieckmann, Y. O. Lee, H. van Liempt, H. von Döhren, H. Kleinkauf, *FEBS Lett*. **1995**, *357*, 212.

enzyme.[189] In this example, module 1 contains a condensation domain (C) as the last domain. In this domain, the new amide bond (as in this example) or ester bond (in depsipeptide synthesis) is formed, elongating the chain.[190] The process is then repeated in module 2: the adenylation domain recognizes the dipeptide product of module 1, activates it and transfers is to the peptide carrier protein. In this example, module 2 contains an additional, non-necessary domain, the epimerization domain (E).[191] This domain is capable of epimerizing the innermost amino acid in the substrate-enzyme complex. There are several other non-necessary domains capable of other chemical transformations, such as *N*-methylation (NMT), cyclization (Cy) or formylation (F) domains.[192] The final condensation domain of module 2 the gives the epimerized tripeptide, which is shown in Figure 3.6 attached to the PCP domain of module 3. After another condensation, module 3 will terminate the NRPS with the thioesterase (TE) domain.[193] The liberated tripeptide could now undergo further post-synthetic transformations.[194] The incorporation of polyketide synthases (PKS) into NRPS has also been shown to occur.[195] The described biochemical process of NRPS has a large substrate scope, and a wide array of modifying domains gives rise to a vast number of natural products occupying a diverse chemical space.

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[189] T. Stachelhaus, A. Hüser, M. A. Marahiel, *Chem. Biol*. **1996**, *3*, 913; D. E. Ehmann, C. A. Shaw-Reid, H. C. Losey , C. T. Walsh, *Proc. Natl. Acad. Sci. U.S.A*. **2000**, *97*, 2509.
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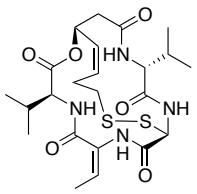
[194] A. M. van Wageningen, P. N. Kirkpatrick, D. H. Williams, B. R. Harris, J. K. Kershaw, N. J. Lennard, M. Jones, S. J. Jones, P. J. Solenberg, *Chem. Biol*. **1998**, *5*, 155; C. T. Walsh, H. Chen, T. A. Keating, B. K. Hubbard, H. C. Losey, L. Luo, C. G. Marshall, D. A. Miller, H. M. Patel, *Curr. Opin. Chem. Biol*. **2001**, *5*, 525.
[195] L. Du, C. Sanchez, M. Chen, D. J. Edwards, B. Shen, *Chem. Biol*. **2000**, *7*, 623; D. E. Cane, C. T. Walsh, *Chem. Biol*. **1999**, *6*, 319.

### 3.3.2 Biological Activities of Depsipeptides

Depsipeptides have been reported to possess a vast range of biological activities.[196] This section will focus on a few selected examples in a medicinal chemistry context and discuss their biological profile in more detail.



**3.05**

**Figure 3.7**: Structure of Romidepsin (**3.05**).

In 2009, the FDA granted approval to the depsipeptide natural product Romidepsin (**3.05**, Figure 3.7) for the treatment of cutaneous T-cell lymphoma. Romidepsin was first isolated and characterized in 1994.[197] It was later discovered that Romidepsin acts as an histone deacetylase (HDAC) inhibitor. The octameric Histone proteins are involved in the packing of DNA, where DNA is wrapped around the Histones.[198] Therefore, these structures must be unwound for gene expression, and this is achieved by acylation of the positively charged lysine residues on the histones by the enzyme histone acetyltransferase (HAT). The reverse process is achieved by HDAC and causes tighter wrapping of the DNA around the histone octamer.[199] HAT and HDAC are opposing forces in a dynamic system to regulate DNA translation and therefore protein expression. It is well known that in cancer cells, HDAC is often overexpressed, causing unfavorable epigenetic changes.[200], therefore counteracting the effect of HDAC overexpression in malignant cells. Romidepsin itself is a prodrug, and it is postulated

[196] B. Hinzen, S. Raddatz, H. Paulsen, T. Lampe, A. Schumacher, D. Häbich, V. Hellwig, J. Benet-Buchholz, R. Endermann, H. Labischinski, *ChemMedChem* **2006**, *1*, 689; N. M. Haste, V. R. Perera, K. N. Maloney, D. N. Tran, P. Jensen, W. Fenical, V. Nizet, M. E. Hensler, *J. Antibiot.* **2010**, *63*, 219; A. K. Ghosh, C. Liu, *Org. Lett.* **2001**, *3*, 635.
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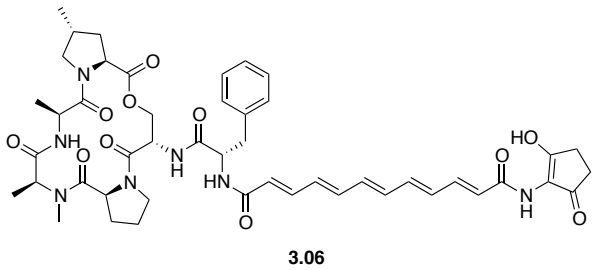
that upon reduction of its disulfide bond in the organism, the formed thiol groups coordinate to a zinc atom present in the HDAC enzyme, thereby inhibiting its activity.[201]

Since the introduction of sulfonamide antibiotics in the 1930s,[202] the therapeutic efficacy of antibiotics has suffered from the emergence of resistant strains. For example, Methicillin-resistant *Staphylococcus aureus* (MRSA) is a multidrug resistant bacterial strain often found in hospitals. It is able to cause severe complications by secondary infections in otherwise low-risk surgeries.[203] Historically, most clinically applied antibiotics rely upon inhibition of critical metabolic processes in bacteria. The β-lactam antibiotic class of penicillins and cephalosporins inhibits cell wall biosynthesis in the bacterium, and resistant mutants have developed β-lactamases to degrade these antibiotics (Section 1.3).[204] Since for possibly every new antibiotic resistance will eventually be observed to a certain extent, antibiotics with new modes of actions are highly sought after. Enopeptin A (**3.06**, Figure 3.8) constitutes a member of a newly found class of antibiotics, the acyldepsipeptide (ADEP) antibiotics.[205]



**3.06**

**Figure 3.8**: Structure of enopeptin A (**3.06**).

Enopeptin A (**3.06**) and several other ADEP antibiotics activate the proteolytic proteasome complex caseinolytic peptidase (ClpP).[205] Since ClpP is involved in the degradation of proteins, it is highly regulated and requires a ClpP-ATPase along with

[201] R. Furumai, A. Matsuyama, N. Kobashi, *Cancer Res.* **2002**, *62*, 4916; J. E. Bradner, N. West, M. L. Grachan, *Nat. Chem. Biol.* **2010**, *6*, 238.
[202] H. Otten, *J. Antimicr. Chemoth.* **1986**, *17*, 689.
[203] K. Hiramatsu, K. Okuma, X. X. Ma, M. Yamamoto, S. Hori, M. Kapi, *Curr. Opin. Infect. Dis*. **2002**, *15*, 407; L. M. Weigel, D. B. Clewell, S. R. Gill, N. C. Clark, L. K. McDougal, S. E. Flannagan, J. F. Kolonay, J. Shetty, G. E. Killgore, F. C. Tenover, *Science* **2003**, *302*, 1569; D. M. Sievert, M. L. Boulton, G. Stoltman, D. Johnson, M. G. Stobierski, F. P. Downes, P. A. Somsel, J. T. Rudrik, W. Brown, W. Hafeez, T. Lundstrom, E. Flanagan, R. Johnson, J. Mitchell, S. Chang, *MMWR Morb. Mortal. Wkly. Rep*. **2002**, *51*, 565; D. Miller, V. Urdaneta, A. Weltman, *MMWR Morb. Mortal. Wkly. Rep*. **2002**, *51*, 902; P. C. Appelbaum, *Clin. Infect. Dis*. **2002**, *34*, 1613.
[204] K. Lewis, *Nat. Rev. Drug Discov.* **2013**, *12*, 371; K.-F. Kong L. Schneper, K. Mathee, *APMIS* **2010**, *118*, 1.
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other activating agents in order to hydrolyze peptides.[206] The inactive heptameric ClpP complex itself only allows for free diffusion of small polypeptides (hexapeptides or smaller) into the proteolytically active chamber formed by the heptamer.[207] ADEP antibiotics such as **3.06** bind to the same active site as the corresponding ClpP-ATPases and therefore cause uncontrolled peptide degradation in the bacterial cell .[208] Since no currently marketed antibiotic drugs target ClpP activation, ADEPs are promising candidates for a new class of antibiotics, and even for the treatment of multidrug resistant strains.[209] Several SAR studies have been conducted and reported for these compounds, underlining the unique biological profiles of depsipeptides.[210]

## 3.4 Aetheramide A and B – HIV-Inhibitory Depsipeptides

Several cyclic depsipeptides with HIV-inhibitory properties have been reported.[211] More recently, the group of Müller reported the isolation and structural elucidation of two cyclic depsipeptides, the aetheramides A and B (**3.07** and **3.08,** Figure 3.9).[212] The depsipeptides were isolated from a recently discovered genus of myxobacteria *Aetherobacter*.[213] More specifically, the strain *Aetherobacter rufus* was cultivated in a yeast medium and bioassay-guided isolation gave the two compounds **3.07** and **3.08**. Similar to other natural products before,[214] it was found that the two isomers are in equilibrium *via* transesterification in a methanolic solution.

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[206] S. Gottesman, E. Roche, Y. Zhou, R. T. Sauer, *Genes. Dev*. **1998**, *12*, 1338; S. K. Singh, R. Grimaud, J. R. Hoskins, S. Wickner, M. R. Maurizi, *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 8898; T. A. Baker, R. T. Sauer, *Trends Biochem. Sci*. **2006**, *31*, 647; J. A. Alexopoulos, A. Guarne, J. J. Ortega, *Struct. Biol*. **2012**, *179*, 202.

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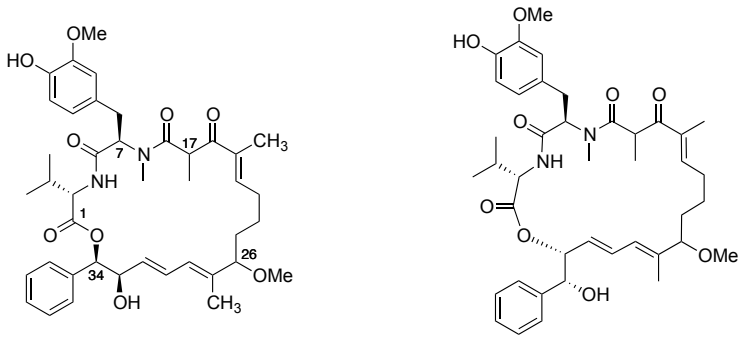
[213] R. Garcia, K. Gerth, M. Stadler, I. J. Jr. Dogma, R. Müller, *Mol. Phylogenet. Evol*. **2010**, *57*, 878.

[214] M. Bock, R. Dehn, A. Kirschning, *Angew. Chem. Int. Ed*. **2008**, *47*, 9134.




**3.07** **3.08**

**Figure 3.9**: Structure of Aetheramide A (**3.07**) and B (**3.08**).

The molecular structure was assigned by HRMS, NMR spectroscopy, Mosher ester analysis and quantum mechanical calculations. The natural products were found to possess a dipeptide fragment consisting of a valine- and an unusual 3-methoxy-*N*-methyl-(*R*)-tyrosine subunit. The valine residue was identified to be connected to an (*R*,*R*)-configured *syn*-diol with a geminal phenyl-group and (*E*,*E*)-configured diene. The absolute configuration of the allylic methyl ether in the C(26) position and of the C(17) of the β-keto amide could not be determined unambiguously. From a synthetic point of view, the absolute conformation could be confirmed by total synthesis, and larger quantities of the compounds for biological studies could be obtained. Furthermore, a suitable retrosynthetic approach would give access to structural analogues for SAR studies. Therefore, we decided to start a total synthesis program to address these challenges. Previous synthetic efforts towards the aetheramides A (**3.07**) and B (**3.08**) are summarized in the next chapter.

## 3.5 Previous Synthetic Contributions

Several Groups have already published their synthetic efforts towards the Aetheramides. The first report of an attempted total synthesis from the Kalesse group is outlined in Scheme 3.1.[215] Starting from the cinnamate **3.09**, the *syn* hydroxyl groups were introduced *via* a Sharpless asymmetric dihydroxylation reaction.[216] The following double TBS protection could render a prospective regioselective esterification on the diol more difficult. A reduction-oxidation-Wittig sequence followed by another reduction-oxidation step furnished the aldehyde **3.10**.

---

[215] C. Jahns, *Ph. D. Thesis,* Gottfried Wilhelm Leibniz Universität Hannover; Germany, **2012**.
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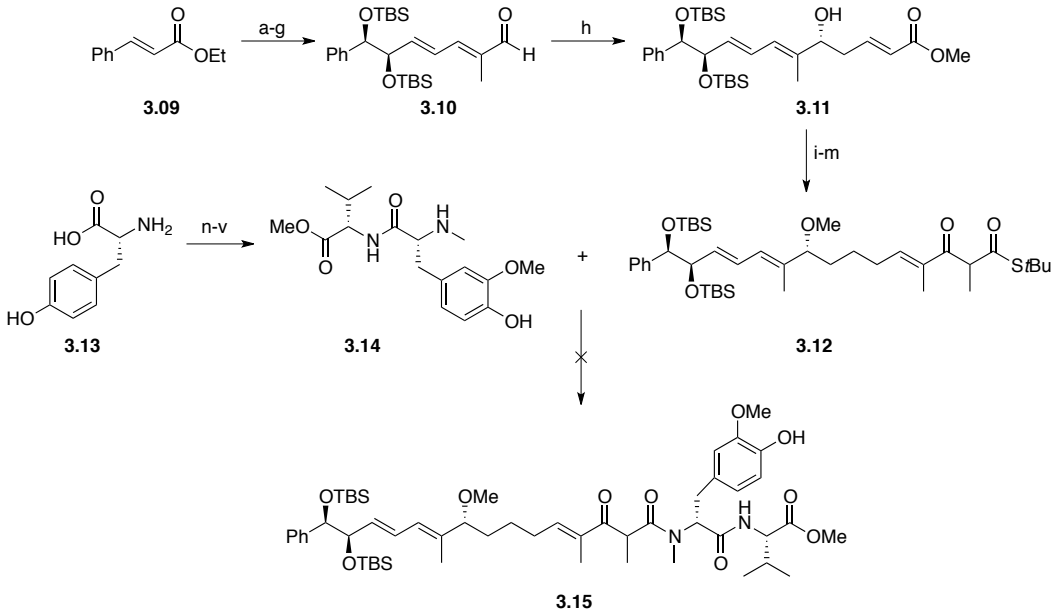


**Scheme 3.1**: Synthesis reported by the Kalesse group. a) AD-β-mix, $MeSO_2NH_2$, 77%; b) TBSOTf, 2,6-lutidine, 96%; c) DIBAL-H, 87%; d) IBX; e) Wittig salt, *n*-BuLi, 62% over two steps; f) DIBAL-H, 89%; g) $MnO_2$; h) VMA, 80% over two steps; i) Meerwein's salt, proton sponge; Stryker's Reagent, $PhSiH_3$, 40% over two steps; j) $NiCl_2$, $NaBH_4$; k) DIBAL-H; l) $MnO_2$, 47% over three steps; m) HWE reagent, KHMDS, 36% n) $AlCl_3$, acetylchloride, 76%; o) $SOCl_2$, MeOH, 70%; p) CbzCl, $Na_2CO_3$, 90%; q) BnBr, $K_2CO_3$, TBAI, 72%; r) *m*CPBA, DCM, $K_2CO_3$, 63%; s) NaH, MeI, quant.; t) LiOH, THE/MeOH/$H_2O$; u) methyl valinate, EDC, HOBt, DIPEA, 75% over two steps; v) $H_2$, Pd/C, 66%.

This then underwent the key step, an enantioselective vinylogous Mukayama-aldol reaction (VMA) under conditions developed by Kalesse and co-workers.[217] The obtained enoate **3.11** was reduced with Stryker's reagent to the aldehyde and then subjected to a final HWE reaction to furnish the thioester **3.12** in 13 steps and 3% overall yield. The thioester was intended to be coupled to the dipeptide fragment **3.14** in a silver-mediated thioester coupling.[218] The synthesis of the dipeptide fragment **3.14** started from commercially available (*R*)-tyrosine (**3.13**), which was acylated, protected and oxidized in a Baeyer-Villiger reaction[219] to give the fully decorated aromatic system according to a literature procedure.[220] A peptide coupling reaction followed by deprotection then gave the fragment **3.14** in 13 steps and 11% overall yield. Unfortunately, the silver mediated thioester coupling of **3.12** and **3. 14** could not be realized, as the thioester **3.12** appeared to be too unreactive.

[217] S. Simsek, M. Horzella, M. Kalesse, *Org. Lett*. **2007**, *9*, 5637.
[218] S. V. Ley, P. R. Woodward, *Tetrahedron Lett*. **1987**, *28*, 3019; G. Zhou, D. Lim, D. M. Colart, *Org. Lett*. **2008**, *10*, 3809; M. C. Bagley, K. Chapaneri, J. W. Dale, X. Xiong, J. Bower, *J. Org. Chem*. **2005**, *70*, 1389; L. T. Burke, D. J. Dixon, S. V. Ley, F. Rodriguez, *Org. Biomol. Chem*. **2005**, *3*, 274.
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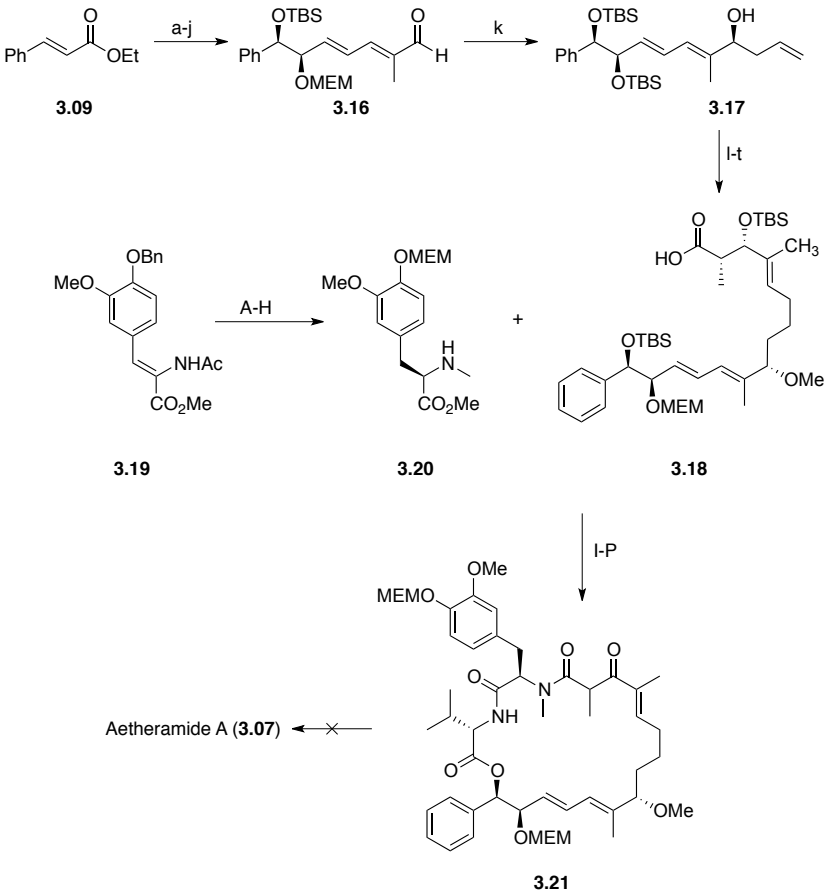


**Scheme 3.2**: Synthesis reported by the Gosh group. a) AD-β-mix, $MeSO_2NH_2$, 82%; b) TBSCl, py; c) MEMCl, DIPEA, 43% over two steps; d) DIBAL-H; e) Swern oxidation; f) Wittig reaction, 76% over 3 steps; g) DIBAL-H; h) Wittig reaction, 83% over two steps; i) DIBAL-H; j) Swern oxidation; k) asymmetric allylation, 55% over three steps; l) NaH, MeI; m) 9-BBN, 71% over two steps; n) MsCl, $NEt_3$; o) NaCN, DMSO, 69% over two steps; p) DIBAL-H; q) Wittig reaction, 65% over two steps; r) Evan's aldol, 82%; s) TBSOTf, 2,6-lutidine; t) LiOH, $H_2O_2$, $H_2O$, 70% over two steps; A) Enantioselective hydrogenation; B) $H_2$, Pd/C, 75% over two steps; C) $MeSO_3H$; D) CbzCl, $NEt_3$; E) $K_2CO_3$, MeOH, 48% over three steps; F) MEMCl, DIPEA; G) MeI, $Ag_2O$; H) $H_2$, $Pd(OH)_2$, 51% over three steps; I) BOPCl, DIPEA, 63%; J) TBAF-AcOH; K) Fmoc-Val, EDC, DMAP, DIPEA, 49% over two steps; L) $Me_3SnOH$; M) MeCN, $Et_2NH$; N) BOPCl, 2,6-lutidine, 47% over two steps; O) TBAF-AcOH; P) DMP, 53% over two steps.

The Ghosh group recently reported the synthesis of a MEM protected derivative **3.21** of Aetheramide A (**3.07**, Scheme 3.2).[221] This synthesis also involved an asymmetric dihydroxylation of cinnamate **3.09** to introduce the *syn*-diol. The hydroxy groups were then selectively protected in rather low yield, but, nevertheless, this allowed for selectively forming one of the two possible esters later in the synthesis. After two Wittig reactions and the corresponding reduction-oxidation steps, the aldehyde **3.16** was obtained. The key step was the introduction of the vinylic stereocenter, which was accomplished *via* an asymmetric allylation with a silver(I)-(*S*)-BINAP complex and

[221] A. K. Ghosh, K. V. Rao, S. Akasapu, *Tetrahedron Lett.* **2014**, *55*, 5191.

allyltributylstannane.[222] Furhter steps involved a hydroboration of the newly introduced double bond and conversion into an aldehyde. This set the stage for an Evan's aldol reaction.[223] After cleavage of the auxiliary and protection, the *syn*-configured acid **3.18** was obtained. The necessety of the Evans aldol reaction was not entirely justified, as the hydroxy group would be oxidized later in the route, and it can be argued that in the natural product, the acidic α-position would equilibrate to the more stable epimer. However, the report does not comment on this. The amino acid **3.20** was synthesized from the known enamide **3.19**[224] *via* an asymmetric hydrogenation. Next, a cascade of protecting group modifications was necessary. This was followed by a final methylation and deprotection to furnish the free amine **3.20**, which was then coupled to the acid **3.18** with BOPCl in 63% yield. The homobenzylic TIPS group was then cleaved in order to introduce the valine residue, and deprotection and macroamidation furnished the macrocyclic core structure. Another TBS deprotection followed by oxidation then gave the MEM protected aetheramide A derivative **3.21**. Unfortunately, the group was not able to remove the MEM groups under acidic conditions, as this caused elimination of the methyl ether followed by decomposition. We took mental note of this in reference to our synthesis, as this elimination might be avoided by formation of the lactone at the benzylic position, giving rise to Aetheramide B (**3.08**). In summary, the approach reported by Ghosh and co-workers gave the MEM protected natural product **3.21** in 36 steps and 0.82% yield. Compared to Kalesses approach, Ghosh's route gave rise to a higher step count. This was due to the linear approach, installing the two amino acid moieties separately, whereas Kalesse's work described the introduction of the dipeptide fragment directly. Most recently, the group of Prasad reported an "expeditious" synthesis of the polyketide fragment of the Aetheramides as presented in Scheme 3.3.[225]

[222] M. Georgy, P. Lesot, J.- M. Campagne, *J. Org. Chem.* **2007**, *72*, 3543; A. Yanagisawa, H. Nakashima, A. Ishiba, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 4723.
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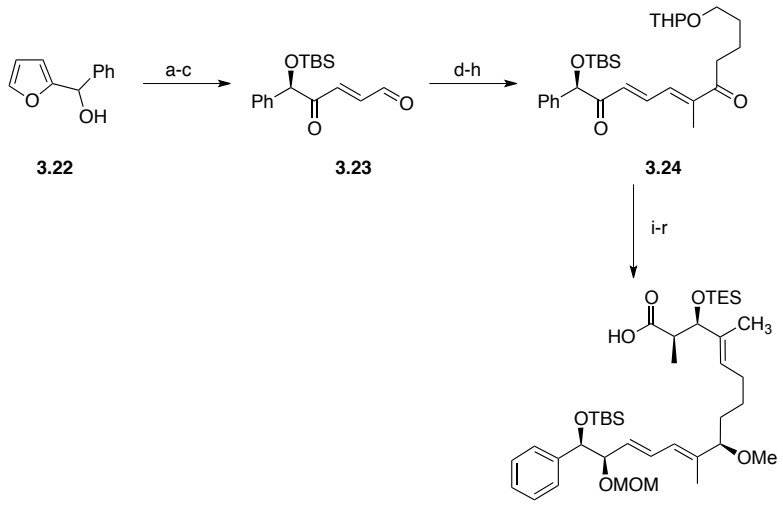
[224] M. S. Matta, A. Kelley, M. F. Rohde, U.S. Patent Application Publication U.S.1973/3878043 A1.
[225] O. Revu, K. Prasad, *Synlett* **2014**, *25*, 2887.

In this synthesis, the racemic furanol **3.22** was initially subjected to Sharpless kinetic resolution conditions[226] to give the desired alcohol in 43% yield and 99% *e.e.* The hydroxyl group was then TBS protected and ring opening of the furan[227] gave the enal **3.23**. Reaction with a Weinreb-amide substituted HWE reagent, followed by a Grignard addition, gave the ketone **3.24**.




**3.22** **3.23** **3.24** **3.25**

**Scheme 3.3**: Synthesis reported by the Prasad group. a) TBHP, Ti(O*i*Pr)$_4$, L-(+)-DIPT, 4 Å MS, 43%, 99% *e.e*; b) TBSCl, imidazole, DMAP, 95%; c) NBS, $NaHCO_3$, 80%; d) HWE reaction, 91%; e) $NaBH_4$, $CeCl_3$, 87%; f) MOMCl, DIPEA, 93%; g) NHMe(OMe)HCl, *i*PrMgCl, 85%; h) $Br(CH_2)_4OTHP$, 83%, i) (*S*)-CBS catalyst, borane dimethyl sulfide complex, 82%; j) NaH, MeI, 80%; k) PPTS, , MeOH, 84%; l) IBX; m) Wittig reaction, 95% over two steps; n) DIBAL-H, 87%; o) $MnO_2$; p) Nagao aldol reaction, 90% over two steps; q) TESOTf, pyridine, 92%; r) LiOH, $H_2O_2$, 60%.

The ketone was then asymmetrically reduced in a CBS-reduction.[228] The *syn*-diol was formed *via* a diastereoselective Luche reduction.[229] THP deprotection and oxidation, followed by Wittig reaction and a reduction-oxidation sequence gave an aldehyde, which was then subjected to a Nagao aldol reaction[230] to give a *syn*-aldol product. Again, the authors did not comment on the necessity of this enantio- and diastereoselective reaction with respect to equilibration of the configuration in the

[226] M. Kusakabe, Y. Kitano, Y. Kobayashi, Y. Sato, *J. Org. Chem.* **1989**, *54*, 2085.
[227] Y. Kobayashi, M. Nakano, G. B. Kumar, K. Kishihara, *J. Org. Chem.* **1998**, *63*, 7505; Y. Kobayashi, G. B. Kumar, T. Kurachi, H. P. Acharya, T. Yamazaki, T. Kitazume, *J. Org. Chem.* **2001**, *66*, 2011.
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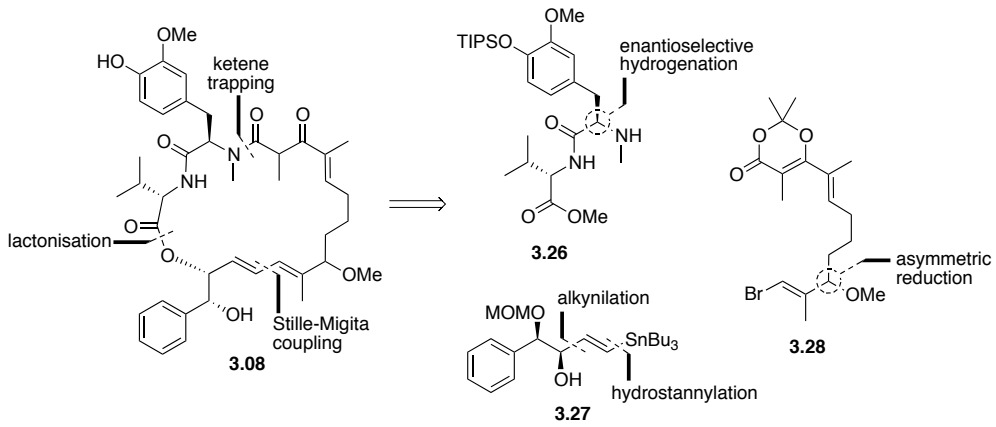
[229] J. L. Luche, *J. Am. Chem. Soc*. **1978**, *100*, 2226; J. L. Luche, L. Rodriguez-Hahn, P. Crabbe, *J. Chem. Soc., Chem. Commun*. **1978**, 601; J. L. Luche, A. L. Gemal, *J. Am. Chem. Soc*. **1979**, *101*, 5848.
[230] Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto, E. Fujita, *J. Org. Chem.* **1986**, *51*, 2391.

natural product. The auxiliary was then cleaved to give the acid **3.25** in 18 steps and 3.8% overall yield. Prasad's approach featured a novel way for the introduction of the *syn*-diol compared to Kalesse and Ghosh's reports, but at the cost of a necessary kinetic resolution at the beginning of the synthesis. The (*R*)-methyl ether was accessed *via* a CBS reduction, which is probably more straightforward than the asymmetric VMA and asymmetric allylation in the other reports. Prasad then also applied an enantio- and diastereoselective Nagao aldol reaction in the late stages of the synthesis of the fragment, similar to Ghosh's synthesis, whereas Kalesse's approach relied upon equilibration of the configuration of the α-position in the natural product.

In summary, the three reported routes followed a rather linear strategy, and only Kalesse's approach featured a more convergent route *via* introduction of a dipeptide fragment **3.14**. The *syn*-diol group was either introduced *via* asymmetric dihydroxylation or kinetic resolution. The β-hydroxy ester functions were introduced with asymmetric aldol reactions in Ghosh and Prasad's synthesis, whereas Kalesse argued in favor of an eventual equilibrium of the absolute configuration in the natural product, rendering an enantio- and diastereoselective approach to this fragment unnecessary. The stereocenter of the methyl ether was accessed by enantioselective allylation (Ghosh), asymmetric VMA (Kalesse) or CBS reduction (Prasad). The unnatural amino acid fragments were accessed by enantioselective hydrogenation in Ghosh's synthesis, and by functionalization of (*R*)-tyrosine as reported by Kalesse.

## 3.6 Retrosynthetic Analysis

Scheme 3.4 illustrates our retrosynthetic analysis of aetheramide B (**3.08**). Our strategy divides the molecule into the three major fragments. This convergent approach allows for a modular synthesis and more general flexibility. The dipeptide fragment **3.26** would be synthesized *via* an asymmetric hydrogenation reaction of an enamide to furnish the unnatural aromatic amino acid moiety. After peptide coupling to (*S*)-valine, the fragment would be attached by esterification and trapping of a ketene derived from dioxinone fragment **3.28**. For the synthesis of fragment **3.28**, we envisioned either a late stage dioxinone-formation of an advanced intermediate or an initial formation of a dioxinone and further decoration of this core.




**Scheme 3.4**: Retrosynthetic analysis of Aetheramide B (**3.08**) and the main fragments **3.26**-**3.28**.

The beauty of dioxinones such as **3.28** lies in their reactivity: upon heating (commonly in toluene, reflux) they release acetone to form a ketene, which can be trapped by various nucleophiles.[231] The dioxinone group therefore acts as an activating group *and* as a synthetic analog to labile β-keto acids, which are prone to decarboxylation. Although the ketene trapping reaction would be expected to show moderate diastereoselectivity at the most, like Kalesse we argue that the conformation in the natural product would equilibrate to the more stable configuration. The stereocenter of the methyl ether would be formed by CBS reduction of the corresponding bromo-enone. It could then be coupled to the stannane fragment **3.27** in a Stille-Migita cross coupling.[232] Fragment **3.27** itself would be synthesized from known MOM protected (*R*)-mandelic aldehyde **3.83** in a Cram chelation-controlled alkynylation,[233] followed by a hydrostannylation reaction. This chiral-pool approach has the advantage that no enantioselective reactions have to be carried out in the synthesis of the diol fragment fragment, as opposed to the syntheses described in the previous sections. The hydrostannylation reaction could also be replaced by a hydroboration reaction for a subsequent Suzuki-Miyaura coupling, allowing for alternative strategies.

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[231] M. Sato, H. Ogasawara, S. Komatsu, T. Kato, *Chem. Pharm. Bull.* **1984**, *32*, 3848; R. J. Clemens, J. A. Hyatt, *J. Org. Chem*. **1985**, *50*, 2431; R. C. F. Jones, M. Tankard, *J. Chem. Soc. Perk. Trans. 1* **1991**, 240; E. A. Crane, T. P. Zabawa, R. L. Farmer, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2011**, *50*, 9112; F. Calo, J. Richardson, A. G. M. Barrett, *Org. Lett.* **2009**, *11*, 4910; N. S. George, K. E. Anderson, A. G. M. Barrett, *Eur. J. Org. Chem.* **2013**, *33*, 7604.

[232] M. Kosugi, K. Sasazawa, Y. Shimizu, T. Migita, *Chem. Lett*. **1977**, 301; M. Kosugi, Y. Shimizu, T. Migita, *Chem. Lett*. **1977**, 1423; M. Kosugi, Y. Shimizu, T. Migita, *J. Organomet. Chem*. **1977**, *129*, 36; D. Milstein, J. K. Stille, *J. Am. Chem. Soc*. **1978**, *100*, 3636; D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4981; D. Milstein, J. K. Stille, *J. Am. Chem. Soc*. **1979**, *101*, 4992; D. Milstein, J. K. Stille, *J. Org. Chem*. **1979**, *44*, 1613.

[233] D. J. Cram, F. A. A. Elhafez, *J. Am. Chem. Soc*. **1952**, *74*, 5828; D. J. Cram, K. R. Kopecky, *J. Am. Chem. Soc.* **1959**, *81*, 2748.

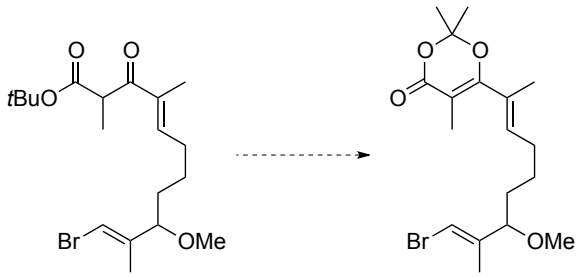
This approach also allows the formation of the macrocycle *via* either intramolecular ketene trapping, macrolactonizaiton or Stille macrocyclization.

## 3.7 Results and Discussion

### 3.7.1 Synthesis of the Eastern Fragment

#### *3.7.1.1 Late Stage Dioxinone Formation*

Our first generation approach involved the late stage formation of the dioxinone **3.28** from the proposed advanced intermediate **3.29,** as shown in Scheme 3.5.




**3.29** **3.28**

**Scheme 3.5**: Proposed late stage dioxinone formation from the advanced intermediate **3.29**.

The synthesis of the advanced intermediate **3.29** started from glutaraldehyde **3.30** and is depicted in Scheme 3.6. A Wittig reaction[234] furnished the known enone **3.31**[235] in acceptable yield and excellent selectivity (*E/Z* > 30:1). For initial studies of the feasibility of our approach, we decided to continue the synthesis with racemic material. Aldehyde **3.31** was therefore alkynylated with trimethylsilylacetylene and *n*-BuLi, followed by methyl ether formation with methyl iodide, *n*-BuLi and DMSO[236] to give ester **3.32** in good to excellent yields. Claisen condensation[237] with either *tert*-butyl propionate or methyl propionate and LDA furnished the β-keto esters **3.33** decent yields. With the stage set for the dioxinone formation, *tert*-butyl ester **3.33** was subjected to standard dioxinone formation conditions ($Ac_2O$, $H_2SO_4$, acetone or TFA-anhydride, TFA, acetone, Scheme 3.6).

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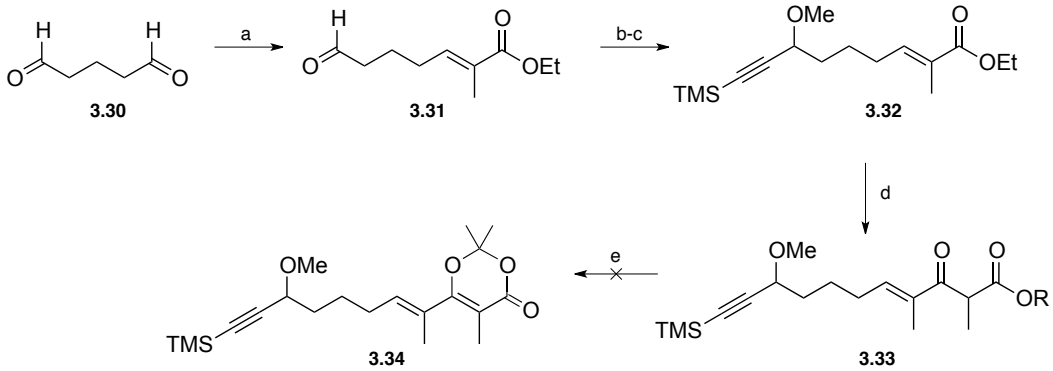
[234] G. Wittig, G. Geissler, *Ann*. **1953**, *580*, 44; G. Wittig, G. U. Schöllkopf, *Chem. Ber*. **1954**, *97*, 1318; G. Wittig, W. Haag, *Chem. Ber*. **1955**, *88*, 1654.
[235] E. L. Richards, P. J. Murphy, F. Dinon, S. Fratucello, P. M. Brown, T. Gelbrich, M. B. Hursthouse, *Tetrahedron* **2001**, *57*, 7771.
[236] J. Gagnepain, E. Moulin, C. Nevado, M. Waser, A. Maier, G. Kelter, H.-H. Fiebig, A. Fürstner, *Chem. Eur. J.* **2011**, *17*, 6973.
[237] L. Claisen, O. Lowman, *Ber*. **1887**, *20*, 651.



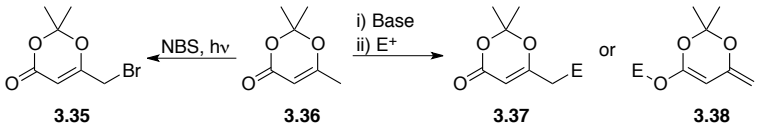

3.30 3.31 3.32 3.33 3.34

**Scheme 3.6**: Synthesis of compound **3.33**. a) $Ph_3P$=C(Me)COOEt, DCM, r.t., 18 h, 58%; b) TMS-acetylene, *n*-BuLi, THF, -78 °C to 0 °C, 4 h, 91%; c) *n*-BuLi, MeI, DMSO, THF, -78 °C to r.t., 18 h, 79%; d) *tert*-butyl propionate or methyl propionate, LDA, THF, -78 °C to 0 °C, 18 h, 57% for R = Me, 68% for R = *t*-Bu; e) $Ac_2O$, $H_2SO_4$, acetone, 0 °C to r.t., 24 h, or TFA-anhydride, TFA, acetone, 0 °C to r.t., 24 h; R = *t*-Bu.

Using sulfuric acid only, we observed TMS-deprotection and decomposition, whereas with TFA and TFA-anhydride, only unreacted starting material was observed, even at elevated temperature. Therefore, we decided to change our strategy to form the dioxinone fragment at an early stage of the synthesis and then further functionalize it.

### *3.7.1.2 Formation and Trapping of Dioxinone Derived Homoenolates*

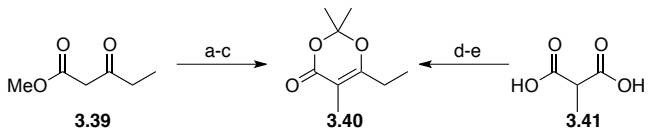
As previous studies have shown, certain dioxinones can undergo deprotonation in the allylic position, and the formed vinylogous enolates can be trapped by an electrophile to form silyl enol ethers, ketones and alcohols,[238] or phosphonates (Scheme 3.7).[239] It has also been reported that dioxinones can be halogenated under Wohl-Ziegler[240] allylic bromination conditions.[241] We therefore strived for the synthesis and further functionalization of dioxinone **3.40** bearing a vinylic methyl and ethyl group (Scheme 3.8).




3.35 3.36 3.37 3.38

**Scheme 3.7**: Reported functionalisations of dioxinones

[238] P. A. Peixoto, A. Boulangé, S. Leleu, X. Franck, *Eur. J. Org. Chem.* **2013**, *35*, 3316.
[239] R. K. Boeckman, T. M. Kamenecka, S. G. Nelson, J. R. Pruftt, T. E. Barta, *Tetrahedron Lett.* **1991**, *32*, 2581.
[240] A. Wohl, *Ber*. **1919**, *52B*, 51; A. Wohl, K. Jaschinowski, *Ber*. **1921**, *54B*, 47; K. Ziegler, A. Spath, E, Schaaf, W. Schumann, E. Winkelmann, *Ann*. **1942**, *551*, 80.
[241] S. Wolfe, S. Ro, Z. Shi, *Can. J. Chem.* **1991**, *79*, 1259.

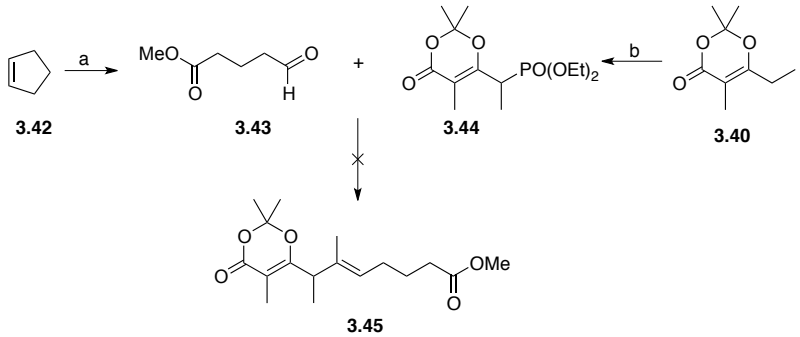



**Scheme 3.8**: Synthesis of building block **3.40**. a) MeI, $K_2CO_3$, THF, 80 °C, 36 h, 97%; b) KOH, MeOH/$H_2O$, r.t. 2 h, 70-93%; c) $Ac_2O$, $H_2SO_4$, acetone, 0 °C to r.t., 4 h, 78%; d) $Ac_2O$, $H_2SO_4$, acetone, 0 °C to r.t., 2 h; propionyl chloride, pyridine, DCM, -78 °C to r.t., 2 h, 38% over two steps; e) acetone, toluene, 190 °C (microwave), 3 h, 31%.

The known building block **3.40**[242] was synthesized *via* two routes (Scheme 3.8). The first synthesis started from methyl-3-oxyvalerate (**3.39**), which underwent methylation with methyl iodide under basic conditions in quantitative yield. In the subsequent saponification of the methyl ester with potassium hydroxide and aqueous methanol, special care had to be taken to prevent decarboxylation of the labile β-keto acid during acidification of the reaction mixture in the aqueous workup and during rotary evaporation of the solvents. Due to these variables, the yields usually varied between 70-90%, but in one case, complete decarboxylation was observed due to an excess of hydrochloric acid in the acidification of the reaction mixture. The obtained acid was usually used immediately without further purification, and standard conditions ($Ac_2O$, $H_2SO_4$, acetone) gave dioxinone **3.40** in good yield.

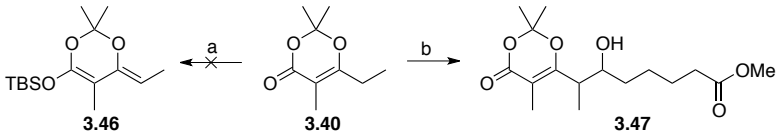
Due to the delicate workup after the ester hydrolysis, we investigated a possibly more facile second route to obtain dioxinone **3.40** (Scheme 3.8, right). Methylmalonic acid (**3.41**) was treated with acetic anhydride and acetone in the presence of a catalytic amount of sulfuric acid, and the obtained Meldrum's acid derivative was acylated with propionyl chloride and pyridine in 38% yield over two steps. Thermal decarboxylation and intramolecular ketene trapping was conducted in a toluene-acetone mixture at 190 °C in a microwave reactor. The reaction proceeded very cleanly according TLC, but the ratio of product/starting material could not be increased beyond 4:3, even by prolonged reaction times or varying solvent mixtures. Separation of the product and starting material by flash chromatography also proved to be challenging due to similar polarities, which lead to a yield of only 31% of product **3.40**. Therefore, we chose to pursue our initial strategy for the synthesis of building block **3.40**.

[242] H. Shimamura, T. Sunazuka, T. Izuhara, T. Hirose, K. Shiomi, S. Ōmura, *Org. Lett.* **2007**, *9*, 65; A. Kamal, A. A. Shaik, S. Azeeza, M. S. Malik, M. Sandbhor, *Tetrahedron: Asymmetry* **2006**, *17*, 2890.




**Scheme 3.9**: HWE reaction to form dioxinone **3.45**. a) Ozone, $NaHCO_3$, DCM/MeOH, -78 °C, 3 h; $NEt_3$, $Ac_2O$, 0 °C to r.t., 2 h, 44%; b) LDA, THF, -78 °C, 1 h; diethyl chlorophosphite, -78 °C to r.t.; $H_2O_2$, DCM, r.t., 1 h, 31%.

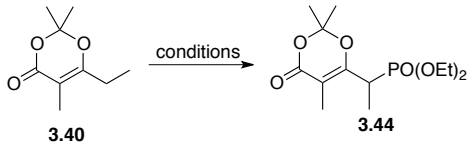
Phosphonate **3.44**[243] was prepared from dioxinone **3.40** and was intended to react in a Horner-Wadsworth-Emmons reaction[136] with aldehyde **3.43**[244] (Scheme 3.9). Cyclopentene (**3.42**) was first subjected to ozone in a DCM-methanol solvent mixture and, after solvent exchange, treated with acetic anhydride in the presence of triethylamine to give aldehyde **3.43** in 44% yield. Although the phosphonation of compound **3.40** is described in literature, we were not able to reproduce the reported yield of 59%.[243] We therefore screened for optimal reaction conditions (Table 3.1). As can be deduced from the results presented in Table 3.1, it can generally be said that the reaction is low in conversion and yield, with a maximum yield of about 30% under optimized conditions (entries 3 and 7). To determine whether this was due to the nature of the nucleophile or the electrophile, we tried to trap the homoenolate with other electrophiles (Scheme 3.10).




**Scheme 3.10**: Trapping of the vinylogous enolates. a) LDA, THF, -78 °C, 1h; TBSCl, -78 °C to r.t., 2 h; b) LDA, THF, -78 °C, 1 h; **3.43**, -78 °C to r.t, 1 h, 39%.

[243] R. K. Boeckman Jr., T. M. Kamenecka, S. G. Nelson, J. R. Prufft, Thomas E. Barta, *Tetrahedron Letters* **1991**, *23*, 2581.
[244] J. Chen, J. Chen, Y. Xie, H. Zhang, *Angew. Chem. Int. Ed.* **2011**, *51*, 1024; R. E. Claus, S. L. Schreiber, *Org. Synth.* **1990**, *64*, 150.

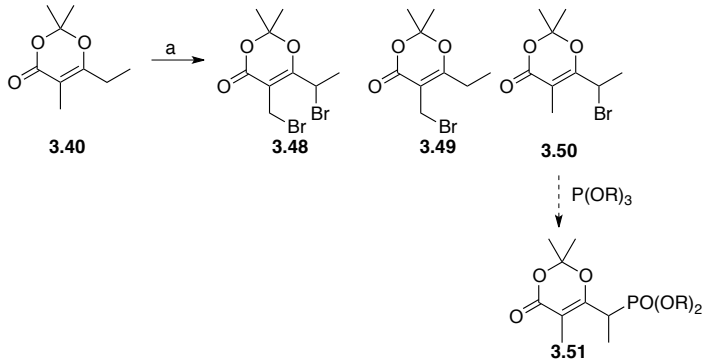
**Table 3.1**: Screening of phosphonation conditions of dioxinone **3.40**.




| Entry | Base (eq.) | $ClP(OEt)_2$ (eq.) | Observation[a] | Yield[b] |
|---|---|---|---|---|
| 1 | DIA (1.2), *n*-BuLi (1.2) | 2.0 | No conversion | – |
| 2 | DIA (1.5), *n*-BuLi (1.5) | 2.0 | Low conversion | 31% |
| 3 | LDA (1.5) [c)] | 2.0 | Low conversion | 28% |
| 4 | LHMDS (1.5) | 2.0 | Low conversion | 10% |
| 5 | HMDS (2.0), *n*-BuLi (2.0) | 2.5 | Low conversion | 20% |
| 6 | HMDS (3.0), *n*-BuLi (3.0) | 3.5 | Low conversion | 18% |
| 7 | HMDS (1.5), *n*-BuLi (1.5) | 2.0 | Low conversion | 28% |

a) According to TLC and $^1$H NMR of the crude product. b) isolated yield. All reaction mixtures were quenched by addition of diethyl chlorophosphite and oxidized by an excess of aqueous $H_2O_2$. c) Commercial solution of LDA in THF/hexanes (1 M).

We were not able to trap the vinylogous enolate with TBSCl, however trapping with aldehyde **3.43** proved to be successful. The observed yield of 39% for the formation of the silyl enol ether was comparable to the yields obtained in the phosphonation reactions (Table 3.1), and concluded that either the deprotonation does not occur readily, or that the vinylogous enolate itself is not reactive enough.

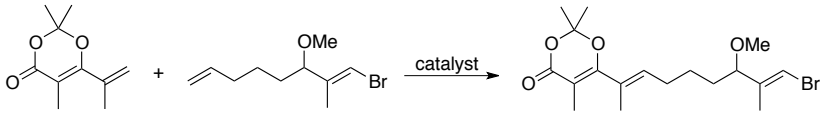



**Scheme 3.11**: Radical bromination of dioxinone **3.40**. a) NBS, AIBN, hν, $CCl_4$, r.t., 1 h, complete conversion.

This hypothesis is supported by the fact that similar reactions were reported to give much higher yield with sterically less hindered dioxinones.[243] The formation of a gel in some reactions might also hint at an undesired polymerization side reaction.

We then tried to brominate **3.40** under Wohl-Ziegler conditions and react the resulting allyl bromide **3.50** with a trialkyl phosphite in order to generate a phosphonate **3.51** in a Michaelis-Arbuzow reaction[245] (Scheme 3.11). The bromination with NBS and AIBN proceeded nicely, but gave an inseparable mixture of the three species **3.48**, **3.49** and **3.50**. We decided to abandon our initially proposed HWE strategy and opted for a new approach presented in the next section.

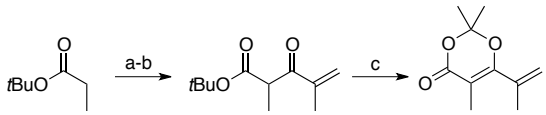
*3.7.1.3 Dioxinone Functionalization by Cross Metathesis*




**3.52** **3.53** **3.54**

**Scheme 3.12**: Functionalisation of dioxinone **3.52** *via* cross metathesis.

Cross metathesis is a powerful synthetic tool to form carbon-carbon double bonds.[246] This methodology has already been successfully used on unsaturated dioxinones in the context of total synthesis.[247] We planed implement cross metathesis in our synthesis as depicted in Scheme 3.12.




**3.55** **3.56** **3.52**

**Scheme 3.13**: Synthesis of dioxinone **3.52**. a) LDA, THF, -78 °C, 30 min; methacrolein, THF, -78 °C, 20 min, 88%; b) IBX, DMSO, r.t., 18 h, 98%; c) TFA, TFA-anhydride, acetone, 0 °C to r.t., 1.5 h, 97%.

Scheme 3.13 illustrates the synthesis of unsaturated dioxinone **3.52**. An aldol addition of *tert*-butyl propionate (**3.55**) to methacrolein furnished a β-hydroxy ester, which was then oxidized by IBX in DMSO to give the β-keto ester **3.56** in excellent yield. Ring closure with TFA and TFA-anhydride in acetone gave dioxinone **3.52** in quantitative yield.

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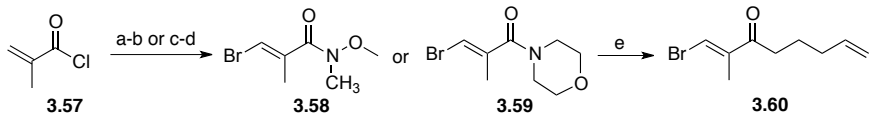
[245] A. Michaelis, T. Becker, *Chem. Ber*. **1897**, *30*, 1003; A. Michaelis, R. Kaehne, *Chem. Ber*. **1898**, *31*, 1048; A. Arbuzov, *J. Russ. Phys. Chem. Soc*. **1906**, *38*, 687; A. Arbuzov, *J. Russ. Phys. Chem. Soc.* **1910**, *42*, 395.

[246] R. R. Schrock, *J. Mol. Catal*. **2004**, *213*, 21; A. H. Hoveyda, R. R. Schrock, *Comprehensive Asymmetric Catalysis* **2004**, *1*, 207; K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.

[247] J. Gebauer, S. Blechert, *J. Org. Chem.* **2006**, *71*, 2021; P. S. Blencowe, A. G. M. Barrett, *Can. J. Chem.* **2012**, *90*, 975.

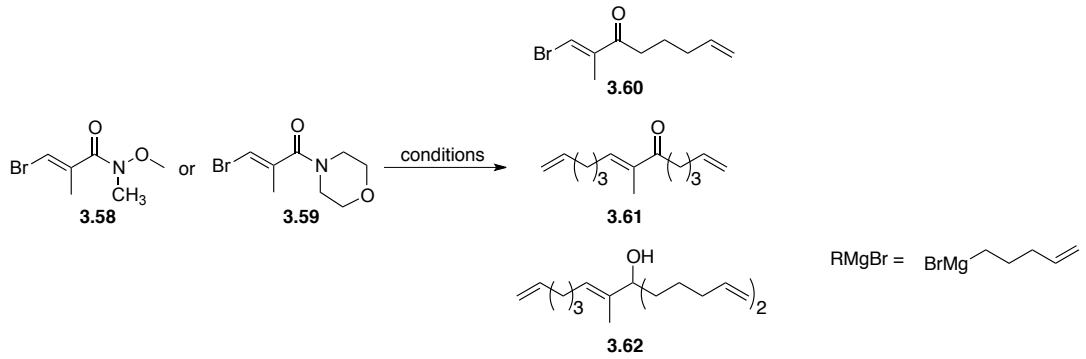



**Scheme 3.14**: Synthesis of fragment **3.60**. a) *N*,*O*-Dimethylhydroxylamine hydrochloride, pyridine, DCM, -20 °C to r.t., 2 h, 93%; b) $Br_2$, DCM, 0 °C, 1 h; DBU, 0 °C to r.t., 2 h, 58%; c) morpholine, pyridine, DCM, -20 °C to r.t., 2 h, 92%; d) $Br_2$, DCM, 0 °C, 1 h; DBU, 0 °C to r.t., 2 h, 28%; e) 5-bromo-1-pentene, Mg, THF, r.t., 30 min; Weinreb amide, THF, 0 °C, 1 h, 29%.

For the synthesis of the allyl ether fragment **3.53** we targeted ketone **3.60** (Scheme 3.14), as it could be directly subjected to asymmetric reduction and methylation to form the desired methyl ether **3.53**. We planned to synthesize bromo-enone **3.60** by Grignard addition[248] of pent-4-enyl-1-magnesium bromide to Weinreb amide[249] **3.58** or **3.59**. It has recently been shown that morpholine amides such as **3.59** can react with Grignard reagents in the same way as Weinreb amides.[250] Therefore, morpholine as well as *N*,*O*-dimethoxyhydroxylamine hydrochloride were acylated by methacryloyl chloride in the presence of pyridine in good yield. Bromination was achieved by a one-pot addition-elimination procedure by first adding a solution of bromine to give the dibromide, followed by addition of DBU to effect β-elimination of HBr. Although these reaction only gave moderate yields, sufficient material for screening the Grignard addition was obtained. The results of this screening are presented in Table 3.2. In all Grignard addition reactions tested, the yield of the desired product never exceeded 30%. Varying the amount of Grignard reagent or changing the solvent had no influence on this outcome. In all cases, byproducts **3.61** and **3.62** were observed, indicating that the enhanced electrophilicity of the bromo enone allowed for 1,4-addition of the nucleophile to occur. Subjecting the morpholine derived amide **3.59** to these conditions gave similar results (entry 5). Additionally, the purified ketone **3.60** proved to be very labile, as it decomposed overnight, even when stored at -20 °C under argon. Therefore, we decided to perform the Grignard addition directly on the Hoecker aldehyde **3.64**[251] and investigate the cross metathesis as depicted in Scheme 3.15.

[248] V. Grignard, *C. R. Acad. Sci*. **1900**, 1322; V. Grignard,. *Ann. Chim*. **1901**, *7*, 433.
[249] S. Nahm, S. M. Weinreb, *Tetrahedron Lett*. **1981**, *22*, 3815.
[250] R. Peters, P. Waldmeier, A. Joncour, *Org. Process Res. Dev.* **2005**, *9*, 508.
[251] X. Li, X. Zeng, *Tetrahedron Lett.* **2006**, *47*, 6839; Y. Murakami, M. Nakano, T. Shimofusa, N. Furuichi, S. Katsumura, *Org. Biomol. Chem.* **2005**, *3*, 1372; J. Hoecker, K. Gademann, *Org. Lett.* **2013**, *15*, 670.

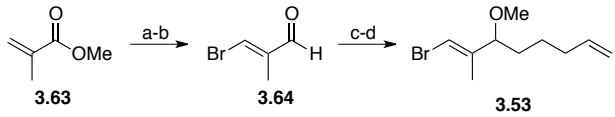
**Table 3.2**: Screening of Grignard addition conditions to Weinreb amides **3.58** and **3.59**.




| Entry | $E^+$ | RMgBr (eq.) | Solvent | Yield of 3.60[a/b] | 3.60:3.61:6.62 |
|---|---|---|---|---|---|
| 1 | **3.58** | 2.0 | THF | 30%[a] | – |
| 2 | **3.58** | 5.0 | THF | 29%[a] | 1:1:1 |
| 3 | **3.58** | 3.5 | THF | 27%[b] | – |
| 4 | **3.58** | 3.5 | $Et_2O$ | 24%[b] | 1:1:1 |
| 5 | **3.59** | 2.0 | THF | 30%[a] | 1:1:1 |

a) isolated yield. b) determined by $^1$H NMR and UPLC-MS analysis of the crude product; RMgBr = pent-4-en-1-ylmagnesium bromide.

The previously developed conditions for the Grignard reaction were found to be suitable for the conversion of aldehyde **3.64** to the alcohol in good yield. Methylation with sodium hydride and methyl iodide gave methyl ether **3.53** in quantitative yield.



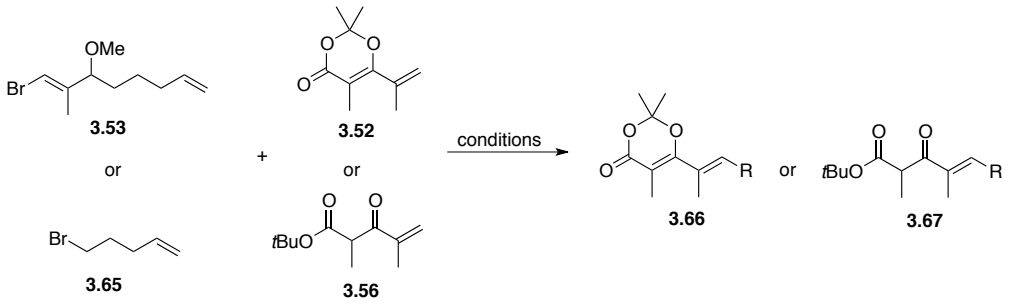

**Scheme 3.15**: Synthesis of fragment **3.53** a) $Br_2$, DCM, 0 °C to r.t., 4 h; DBU, DCM, r.t., 18 h, 94%; b) $LiAlH_4$, $Et_2O$, 0 °C to r.t., 2 h; $MnO_2$, DCM, r.t., 2-5 d, 92%; c) 5-bromo-1-pentene, Mg, THF, r.t., 30 min; **3.64**, THF, 0 °C, 1 h, 72%; d) NaH, MeI, THF, 0 °C to r.t., 30 min, 97%.

We then continued with the investigation of the cross metathesis (Table 3.3). The first three entries indicate an inherent inertness of the subtrates **3.52** and **3.53** in the presence of Grubbs-Hoveyda 2$^{nd}$ generation catalyst and varying alkene stoichiometry. We suspected two main reasons for this observation. First, the possibility of vinyl halides poisoning the catalyst has been reported in the literature,[252] although there are examples

[252] I. C. Stewart, C. J. Douglas, R. H. Grubbs, *Org. Lett.* **2008**, *10*, 441; A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783; V. Sashuk, C. Samojłowicz, A. Szadkowska, K. Grela, *Chem. Commun.* **2008**, *23*, 2468.

where this did not inhibit reactivity.[253] Secondly, sterically hindered and electron deficient substrates have been found to be less reactive in cross metathesis reactions in some cases.[254] However, steric hindrance on an alkene can also have beneficial aspects in cross metathesis, as it can prevent homocoupling.[254] Bearing in mind that cross metathesis on unsaturated dioxinones had been reported before,[247] we continued our screening effort.

**Table 3.3**: Screening of cross metathesis conditions to form.




| Entry | Catalyst (eq.) | Alkene (eq.) | Alkene (eq.) | Observation |
|---|---|---|---|---|
| 1 | GH-2 (0.05) | **3.53** (1.0) | **3.52** (1.0) | No conversion |
| 2 | GH-2 (0.05) | **3.53** (1.0) | **3.52** (2.0) | No conversion |
| 3 | GH-2 (0.05) | **3.53** (2.0) | **3.52** (1.0) | No conversion |
| 4 | GH-2 (0.05) | **3.65** (1.0) | **3.52** (1.0) | Dimerization of **3.65** |
| 5 | GH-2 (0.05) | **3.53** (1.0) | – | No conversion |
| 6 | GH-2 (0.05) | **3.65** (1.0) | **3.56** (2.0) | Dimerization of **3.65** |
| 7 | SF-1 (0.10) | **3.53** (1.0) | **3.52** (2.0) | No conversion |
| 8 | SF-1 (0.10) | **3.65** (1.0) | **3.52** (2.0) | Dimerization of **3.65** |
| 9 | SF-1 (0.10) | **3.65** (1.0) | **3.56** (2.0) | Dimerization of **3.65** |
| 10 | GH-1 (0.05) | **3.65** (1.0) | **3.52** (1.0) | Dimerization of **3.65** |

Abbreviations: GH-1 and GH-2: Grubbs-Hoveyda 1st and 2nd generation catalyst; SF-1: Schrock-Fürstner type catalyst 1.

To prove wether the presence of a vinyl halide was detrimental for the reaction, we performed cross metatheses using 5-bromo-1-pentene **3.65**, and only dimerization of the

[253] A. Fürstner, *Angew. Chem., Int. Ed.* **2000**, *39*, 3013; R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413.
[254] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360.

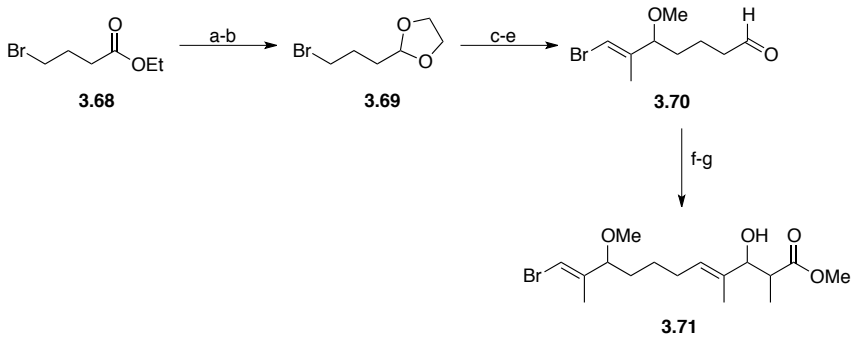
latter was observed. This indicates that the vinyl bromide present in compound **3.53** might poison the catalyst, as for this alkene no dimerization was observed (entry 5). To investigate the effect of steric hindrance in the substrates, we subjected enone **3.56** to our standard conditions and only observed dimerization (entry 6). Reaction with Grubbs-Hoveyda 1st generation catalyst gave the same result (entry 10). We then investigated the suitability of molybdenum-based Schrock-type catalysts.[246] Recent developments by the Fürstner group have rendered these rather sensitive compounds more manageable by attaching a bipyridyl- or phenanthroline dummy ligand to give largely air stable pre-catalysts, which are then converted to the catalytically active species by the addition of dry zinc triflate.[255] Unfortunately, when applied to our system, the same trends as for the ruthenium-based catalysts were observed (entries 7-9).

In conclusion, our strategy to employ a dioxinone structure in fragment **3.28** proved to be unsuccessful. Functionalisations of the dioxinones **3.40** and **3.52** *via* phosphonation and HWE reaction, aldol addition, bromination and cross metathesis were either low-yielding or gave no conversion at all. We attribute these findings to the high steric demand of the dioxinones **3.40** and **3.52**. Furthermore, the vinyl bromide substituent proved to be detrimental to our cross metathesis reactions. Therefore, we decided to abandon this route completely and chose a more classical approach, which will be described in the next section.

### *3.7.1.4 Final Approach via a Wittig-Aldol Sequence*

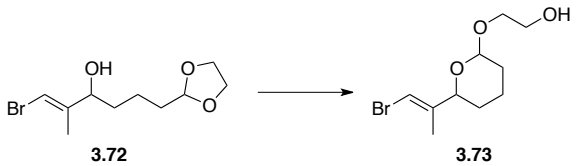
Scheme 3.16 depicts our revised synthetic approach towards the eastern fragment. Harking back to our previously gained synthetic experience, we decided to start from Hoecker aldehyde **3.64** and prepare intermediate **3.70** *via* a Grignard addition and further modifications. A Wittig reaction followed by an aldol addition[256] would then give fragment **3.70**, which would be coupled to the other fragments in a Stille-Migita coupling and peptide coupling reaction. For screening purposes, we decided to initially perform a racemic synthesis (Scheme 3.16).

[255] J. Heppekausen, A. Fürstner, *Angew. Chem. Int. Ed.* **2011**, *50*, 7829.
[256] R. Kane, *J. Prakt. Chem*. **1838**, *15*, 129; R. Kane, *Ann. Phys. Chem. Ser. 2* **1838**, *44*, 475.




**Scheme 3.16**: 3rd approach to fragment **3.70**. a) DIBAL-H, DCM, -78 °C, 2 h; b) ethylene glycol, *p*-TsOH, toluene, Dean-Stark trap, reflux, 1 d, 51% over two steps; c) Mg, THF, r.t., 30 min; **3.69**, THF, 0 °C, 2 h, 79%; d) NaH, MeI, THF, 0 °c to r.t., 30 min, 91%; e) *p*-TsOH, acetone, $H_2O$, 100 °C, microwave, 40 min, 90%; f) $Ph_3P$=C(Me)CHO, DCM, toluene, 65 °C, 3 d, 50%, *E*/*Z*>30:1; g) methyl propionate, LDA, THF, -78 °C, 30 min; aldehyde, THF, -78 °C , 30 min, 50%.

Protected aldehyde **3.69** was synthesized according to a literature procedure.[257] Ethyl-4-bromobutyrate (**3.68**) was reduced to the corresponding aldehyde with DIBAL-H and the crude material was directly protected as an acetale **3.69** in acceptable yield. Grignard addition of dioxolane **3.69** to aldehyde **3.64** proceeded in good yields. The obtained allylic alcohol turned out to be unstable, as partial transketalization of **3.72** to **3.73** was observed within two weeks of storing the compound at 5 °C (Scheme 3.17).

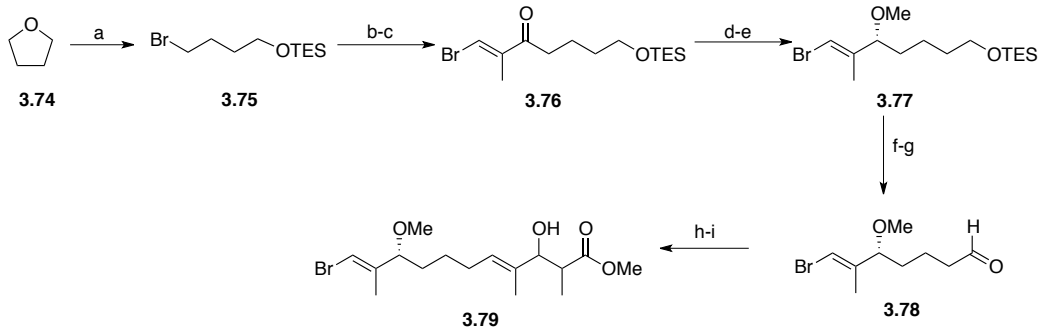



**Scheme 3.17**: Observed transketalization of dioxolane **3.72** to **3.73**.

Thus, the methyl group was introduced preferably in direct succession of the Grignard addition by alkylation with methyl iodide in almost quantitative yield. The dioxolane group was then cleaved by a catalytic amount of *para*-toluenesulfonic acid in an acetone-water mixture under microwave heating (100 °C). Unfortunately, this deprotection always stalled at about 80% conversion to give an inseparable mixture of product and starting material. Efforts to drive the reaction to completion by adding more acid, prolonging reaction time or changing the solvent system proved to be ineffective. We then directly applied this mixture in the following Wittig reaction with a literature known phosphorane.[258] This olefination reagent directly gave an aldehyde in moderate

[257] G. N. Varseev, M. E. Maier, *Org. Lett.* **2005**, *7*, 3881.
[258] M. Engman, P. Cheruku, P. Tolstoy, J. Bergquist, S. F. Völker, P. G. Andersson, *Adv. Synth. Catal.* **2009**, *351*, 375; S. -I. Kiyooka, M. A. Hena, *J. Org. Chem.* **1999**, *64*, 5511.

yield, and the usual reduction-oxidation sequence required in ester stabilized phosphoranes or phosphonates could be circumvented. Finally, aldol addition of methyl propionate to this aldehyde under our previously established conditions gave β-hydroxy ester **3.71** in good yields as a separable diastereomeric mixture (2:1). Reports of similar substrates indicate the relative configuration of the major product to be *anti*.[259] Although we now finally had access to fragment **3.71** in synthetically useful quantities, we decided to perform one last round of optimization of this synthesis to eliminate its major drawbacks, e.g. the tendency of dioxolane **3.72** to undergo transketalization and the inseparability of some intermediates. A TES protected primary alcohol was found to be an ideal replacement for the acetal protecting group in the final synthetic route towards enantiomerically enriched building block **3.79** (Scheme 3.18).




**Scheme 3.18**: Optimized synthesis of enantiomerically enriched fragment **3.80**. a) allyl bromide, triethyl silane; $PdCl_2$, 70 °C, 18 h, 76%; b) Mg, THF, r.t., 30 min; **3.75**, THF, 0 °C, 2 h, 68%; c) TPAP, NMO, 3 Å molecular sieve, DCM, 0 °C to r.t., 30 min, 71%, 91% brsm.; d) (*S*)-CBS catalyst, borane dimethylsulfide complex, toluene, -70 °C to 0 °C, 2 h, e.r. 98:2; e) NaH, MeI, THF, 0 °c to r.t., 30 min, 87% over two steps; f) TBAF, THF, r.t., 1 h, 94%; g) IBX, DMSO, r.t., 18 h, 90%; h) $Ph_3P$=C(Me)CHO, DCM, benzene, 90 °C, 18 h, 95%, *E*/*Z*>30:1; i) methyl propionate, LDA, THF, -78 °C, 30 min; aldehyde, THF, -78 °C , 30 min, 81%.

Tetrahydrofuran (**3.74**) underwent a bromosilation reaction to give the TES-protected alcohol **3.75** in good yield.[260] Palladium(II) chloride must be added last to the reaction, as otherwise thermal excursion of the reaction mixture ensues. Similar to our previous syntheses, we performed a Grignard addition to furnish the corresponding alcohol in good yield. Also in this case we observed decomposition of this alcohol within one week at 5 °C, and we identified the degradation pathway as silyl migration from the primary to the secondary alcohol. Therefore, the alcohol was immediately oxidized under the

[259] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920; C. Palomo, M. Oiarbide, J. M. García*, Chem. Eur. J.* **2002**, *8*, 36.
[260] J. Ohshita, A. Iwata, F. Kanetani, A. Kuna, *J. Org. Chem*. **1999**, *64*, 8024.

conditions developed by Ley and Griffith with TPAP and NMO to give the very labile bromo enone **3.76** in good yield. Enone **3.76** decomposed completely when stored at 5 °C over night. As a result, the compound **3.76** was immediately treated it with (*S*)-CBS catalyst and borane dimethylsulfide complex in dry toluene at -70 °C to give the enantiomerically enriched (e.r. = 98:2) *R*-configured alcohol **3.81** in quantitative yield. Since the mechanism and stereochemical outcome of this reaction have been extensively studied,[261] we did not experimentally confirm the absolute configuration, but only determined the enantiomeric ratio of the alcohol. The chiral HPLC traces of the racemate **3.80** and enantiomerically enriched alcohol **3.81** are shown in Figure 3.10.

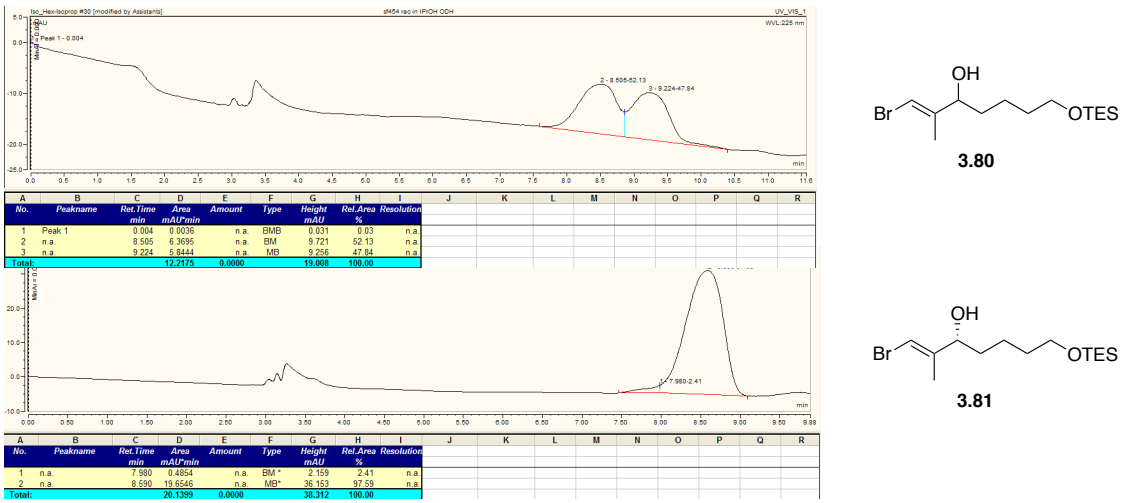



**Figure 3.10**: Chiral HPLC traces of the racemate **3.80** (up) and enantiopure compound **3.81** (below).

The crude material was then directly methylated in high yield with methyl iodide in the presence of sodium hydride to form the stable methyl ether **3.77**. The TES group of ether **3.77** could be cleaved in the work-up of the methylation by adjusting to pH = 1 with aqueous hydrochloric acid, but the reaction was found to be difficult to drive to completion. Furthermore, we wanted to fully characterize the first stable intermediate after four synthetic steps, and therefore decided to remove the TES group in a separate step with TBAF in THF.

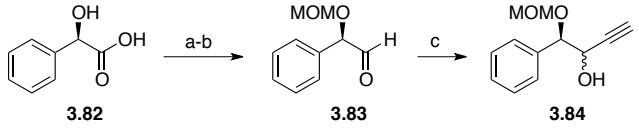
[261] B. Ganem, *Chemtracts: Org. Chem*. **1988**, *1*, 40; S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475; L. Deloux, M. Srebnik, *Chem. Rev*. **1993**, *93*, 763; V. Nevalainen, *Tetrahedron: Asymmetry* **1991**, *2*, 63; L. P. Linney, C. R. Self, I. H. Williams, *J. Chem. Soc., Chem. Commun*. **1994**, 1651; L. P. Linney, C. R. Self, I. H. Williams, *Tetrahedron: Asymmetry* **1994**, *5*, 813; G. J. Quallich, J. F. Blake, T. M. Woodall, *J. Am. Chem. Soc*. **1994**, *116*, 8516.

The crude primary alcohol was oxidized with IBX in DMSO to yield primary aldehyde **3.78**. The next two steps were identical to those of the racemic substrate. Nevertheless, we managed to improve the yield of the Wittig reaction to form the corresponding enal to 95% yield and with complete *E*-selectivity by raising the temperature and changing the solvent mixture from toluene to DCM-benzene. The yield of the final enolate addition to form the fragment **3.79** was improved to a very satisfactory 81% (2:1 d.r.), and we attribute this to the more reliable preparation of LDA on a larger scale (3.5 g of aldehyde were applied in the highest yielding batch).

In summary, we have developed a synthesis of fragment **3.79** from methyl methacrylate **3.63** in 11 steps with 24% overall yield and an e.r. of 98:2 on a multigram scale. Careful execution of the reactions allowed this to be accomplished with only three chromatographic purifications following the Grignard addition, Wittig reaction and the aldol addition.

### 3.7.2 Synthesis of the Diol Fragment

As described in the retrosynthetic analysis (section 3.6), we planned to synthesize the diol fragment **3.27** *via* a Cram chelation-controlled alkynyl anion addition to the known aldehyde **3.83**.[262]



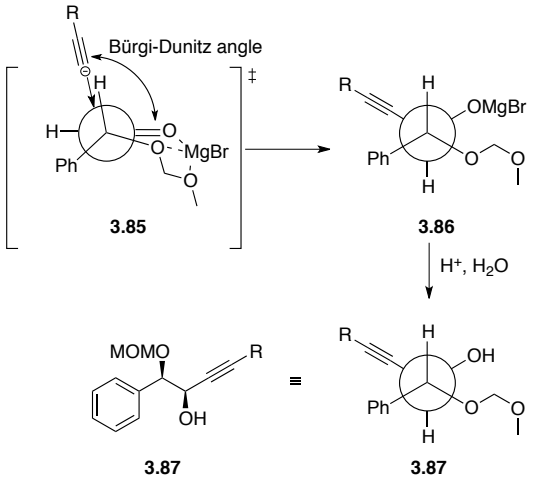

**3.82** **3.83** **3.84**

**Scheme 3.19**: Synthesis of alcohol **3.84**. a) MOMCl, DIPEA, DCM, 40 °C, 18 h, 93%; b) DIBAL-H, DCM, -78 °C, 2 h, 76-98%; c) ethynylmagnesium bromide, THF, -78 °C to r.t., 1 h, 81%, *syn*:*anti* 3:2.

The sequence started from *R*-mandelic acid (**3.82**, Scheme 3.19).[263] Introduction of the coordinating MOM group for the chelation-controlled alkynylation was conducted according to a literature procedure with MOMCl and Hünig's base[264] in DCM in good yield.

[262] E. J. Corey, F. J. Hannon, N. W. Boaz, *Tetrahedron* **1989**, 45, 545.
[263] Parts of the described syntheses were performed by Christopher Wittwer during the course of his master thesis "*Synthetic Studies towards Aetheramide A"*, Christopher Wittwer. Master Thesis, **2014**, University of Basel.
[264] S. Hünig, M. Kiessel, *Chem. Ber*. **1958**, *91*, 380.

Careful monitoring of the reaction temperature in the following DIBAL-H reduction allowed obtaining the aldehyde **3.83** in quantitative yield after aqueous workup. In some cases, however, incomplete reduction or over-reduction occurred, lowering the yield to 76% and making chromatographic purification necessary. We then proceeded with the Cram chelation-controlled alkynylation.

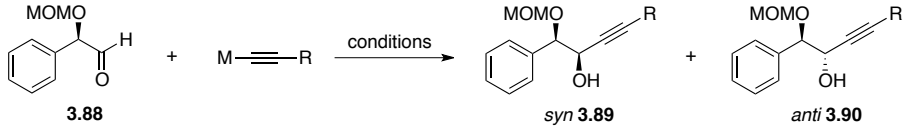



**Scheme 3.20**: Stereochemical model for the diastereoselective alkynylation reaction of **3.83**.

Our stereochemical rationale for the selectivity of this reaction is outlined in Scheme 3.20. The key for 1,2-asymmetric induction in this reaction is the initial formation of a Cram-chelate as depicted in transition state **3.85**, where the magnesium coordinates to the carbonyl function and the oxygen atoms of the α-MOM ether, bringing the two substituents to an eclipsed conformation. The alkynyl anion then attacks the aldehyde from the less hindered half space at the Bürgi-Dunitz angle.[265] Next, the formed alkoxide **3.86** is protonated upon aqueous workup to give the desired *syn*-diol **3.87**. The formation of the chelate complex can be favored by using more strongly coordinating zinc- or magnesium based nucleophiles (compared to Li-nucleophiles), and the presence of a coordinating group such as a MOM ether in the α-position is essential.

[265] H. B. Bürgi, J. D. Dunitz, J. M. Lehn, G. Wipff, *Tetrahedron,* **1974**, *30*, 1563.

**Table 3.4**: Screening of chelation controlled alkynylation conditions of **3.88**.




| Entry | M = (additive) | R = | Conditions | *Syn*/*anti*[a] (% yield) |
|---|---|---|---|---|
| 1 | MgBr | H | THF, -78 °C to r.t., 1 h | 3:2 (81 %) |
| 2 | MgBr; ($ZnBr_2$) | H | THF, -78 °C to r.t., 48 h | 1:1 (–) |
| 3 | MgBr; ($ZnCl_2$) | H | THF, -78 °C to r.t., 48 h | 1:1 (–) |
| 4 | Li | TIPS | $Et_2O$, -78 °C to r.t., 14 h | 7:1 (–) |
| 5 | Li; ($ZnBr_2$) | TIPS | $Et_2O$, -78 °C to r.t., 14 h | 1:1 (–) |
| 6 | Li | TMS | $Et_2O$, -78 °C to r.t., 14 h | 3:1 (–) |
| 7 | Li; ($ZnBr_2$) | TMS | $Et_2O$, -78 °C to r.t., 14 h | 3:1 (–) |

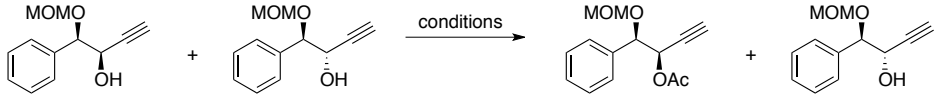
a) Determined by $^1$H NMR analysis of the crude product.

Table 3.4 summarizes our screening efforts for this reaction. Initial experiments with commercially available ethynylmagnesium bromide solution gave an inseparable 3:2 mixture of the diastereomers **3.89** and **3.90** in good yield (entry 1). It is well known that transmetalation from magnesium to stronger coordinating metals such as zinc can improve the diastereoselectivity in Cram-chelation controlled reactions.[266] In this case transmetalation led to decreased reaction rates (48 h vs. 1h) and lower selectivity (entries 2 and 3 vs. entry 1). Another method to increase the *syn*:*anti* selectivity is to use sterically more demanding nucleophiles[267] (entries 4–7). Since the corresponding Grignard reagents were not commercially available, the alkynes were first deprotonated by *n*-BuLi and then used directly (entries 4 and 6) or transmetalated by stirring with zinc bromide (entries 5 and 7). The best diastereoselectivities were observed with the sterically most demanding TIPS-protected alkyne, but surprisingly with the supposedly less chelating organolithium nucleophile as compared to the magnesium- and zinc nucleophiles.

[266] K. T. Mead, *Tetrahedron* **1987**, *28*, 1019; M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, *9*, 2199.
[267] Review articles: A. Mengel, O. Reiser, *Chem. Rev*. **1999**, *99*, 1191; B. W. Gung, *Tetrahedron* **1996**, *52*, 5263; D. J. Ager, M. B. East, *Tetrahedron* **1992**, *48*, 2803; M. T. Reetz, *Angew. Chem. Int. Ed.* **1984**, *23*, 556; P. Wipf, Y. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 11678.

An increased reaction time was also necessary, and ,unfortunately, the crude propargylic alcohols containing a silyl protecting group decomposed during chromatographic purification on silica gel. Albeit giving the best selectivities, the cumbersome workup rendered this approach less attractive, and also the diastereomers were inseparable by flash chromatography. We continued the synthesis with the procedure described in entry 1 and tried to develop a method to separate the diastereomers. We chose an approach based on kinetic resolution with polymer-supported lipase in presence of an acyl donor, as these reactions are usually operationally simple, easily scalable and highly selective[268] and thus performed a screening (Table 3.5).

**Table 3.5**: Screening of reaction conditions for kinetic resolution of **3.89**.




**3.89** **3.90** **3.91** **3.90**

| Entry | Solvent | Acyl donor | Lipase | Conversion[a] |
|---|---|---|---|---|
| 1 | toluene | vinyl acetate | CAL-B | 79% |
| 2 | hexane | vinyl acetate | CAL-B | 85% |
| 3 | toluene | isopropenyl acetate | CAL-B | 68% |
| 4 | hexane | isopropenyl acetate | CAL-B | 72% |
| 5 | toluene | vinyl acetate | CAL-B | 71% |
| 6 | hexane | vinyl acetate | Novozyme 435 | 18% |

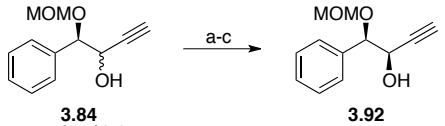
General conditions: diastereomeric mixture of alcohols **3.89** and **3.90** (0.1 mM), acyl donor (3.5 eq.), lipase (10 wt.% of alcohol), r.t.; CAL-B: *Candida antarctica* lipase B; Novozyme 435: a different brand of polymer bound CAL-B. a) determined by $^1$H NMR analysis of an aliquot after 4 d; 100% conversion correspond to complete consumption of protected *syn* diol **3.89**.

Novozyme 435 proved to be rather unsuitable for this reaction (entry 6), although it should be noted that, as with CAL-B, the yield was highly dependent on the source of the used reagent (data not shown). This might be caused by a higher content of absorbed water in the older bottles, which in some cases has been reported to be detrimental for kinetic resolutions of alcohols.[269] Degradation of the enzyme might also account for this observation. Varying the acyl donor or switching the solvent from toluene to hexane did

[268] F. Theil, J. Weidner, S. Ballschuh, A. Kunath, H. Schick, *J. Org. Chem.* **1994**, *59*, 388; L. Poppe, L. Novàk, M. Kajtár-Peredy, C. Szántay, *Tetrahedron: Asymmetry* **1993**, *4*, 2211; A. Ghanem, H. Y. Aboul-Enein, *Chirality* **2004**, *17*, 1.
[269] A. Zaks, A. Klibanov, *J. Biol. Chem.* **1988**, *263*, 8017.

not change the reaction outcome considerably (entries 1–5). The obtained acetate **3.91** and free alcohol **3.90** were readily separated by column chromatography, and the final reaction conditions employed are shown in Scheme 3.21 for the scale up of the reaction (5 g of diastereomeric alcohol mixture).

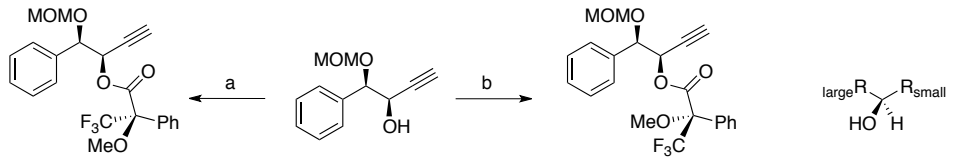
The use of only 10 wt. % of lipase is probably the main cause for the long reaction time of six days, as literature procedures often describe the use of 100 wt.% of lipase resin.[270] Hydrolysis of the acetate with potassium carbonate furnished the diastereomerically pure alcohol **3.92** in quantitative yield (Scheme 3.21).




**3.84** *syn*/*anti* 3:2 **3.92**

**Scheme 3.21**: Kinetic resolution of the alcohol **3.84**. a) CAL-B (10 wt. %), vinyl acetate, hexane, r.t. 6 d, 96% based on *syn*-diol in the starting material; b) $K_2CO_3$, MeOH/$H_2O$, r.t., 20 min, 98 %.

We had yet to experimentally ascertain the absolute configuration of the alcohol **3.92**. Up until now, our stereochemical predictions were solely based on the mechanistic understanding of the Cram-chelation controlled alkynylation (*vide supra*) and the general structure of the faster reacting diastereomer (**3.95**, Scheme 3.22 right) in a lipase catalyzed kinetic resolution according to Kazlauskas' rule.[271] Our initial attempts to form nitrobenzoates from **3.92** for easier crystallization failed, as the isolated products were oily liquids, which we were unable to precipitate or crystallize. We therefore decided to determine the relative configuration by Mosher ester analysis.[272]




**3.93** **3.92** **3.94** **3.95**

**Scheme 3.22**: Formation of the Mosher esters **3.93** and **3.94**. a) *S*-(+)-MTPACl, pyridine, DCM, r.t. 15 h, 95%; b) *R*-(–)-MTPACl, pyridine, DCM, r.t. 15 h, 98%. General structure (**3.95**, right) of the faster reacting enantiomer in a lipase catalyzed kinetic resolution according to Kazlauskas rule.

[270] A. Ghanem, H. Y. Aboul-Enein, *Chirality* **2004**, *17*, 1.
[271] R. J. Kazlauskas, N. E. Weissfloch, A. T. Rappaport, L. A. A. Cuccia, *J. Org. Chem.* **1991**, *56*, 2656.
[272] J. A. Dale, H. S. Mosher, J. *Am. Chem. Soc*. **1973**, *95*, 512; J. A. Dale, H. L. Dull, H. S. Mosher, *J. Org. Chem*. **1969**, *34*, 254; R Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451.

The syntheses of the Mosher esters **3.93** and **3.94** were achieved by acylation with *R*- or *S*-MTPACl in the presence of pyridine in DCM in almost quantitative yield (Scheme 3.22). We then compared the $^{1}$H-$\Delta\delta^{SR}$ values of the two Mosher esters **3.93** and **3.94** (Figure 3.11**)**. It should be noted that (*R*)-MTPACl does give the (*S*)-Mosher ester, since the Cahn-Ingold-Prelog priority[273] changes when the chlorine is substituted by oxygen.

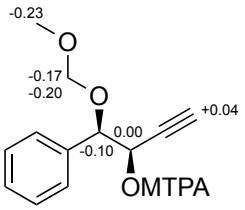
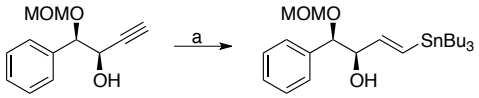



**Figure 3.11**: $\Delta\delta^{SR}$ values of the Mosher esters **3.93** and **3.94**.

The results show a negative $\Delta\delta^{SR}$ for most of the proton signals, which clearly indicates the desired (*R*)-configured propargylic alcohol **3.92** as the major product of the chelation-controlled alkynylation. This finding is also in line with the assumption that the faster acylated alcohol in the kinetic resolution should be (*R*)-configured.[271]




**3.92** **3.27**

**Scheme 3.23**: Hydrostannylation of the propargylic alcohol **3.92**. a) $Pd(PPh_3)_2Cl_2$, $HSnBu_3$, THF, 0 °C, 30 min, 58%, *E*/*Z* = 10:1.

The final step to complete the synthesis of fragment **3.27** was to introduce the vinyl stannane (Scheme 3.23). We initially observed decent yield and *E*/*Z* selectivities for this reaction under standard conditions with a catalytic amount bis(triphenylphosphine) palladium(II) chloride and tributyltin hydride (1.5 eq.).[274] The product expectedly proved to be relatively labile; flash chromatography had to be conducted with an eluent containing 0.5 % triethylamine to suppress protodestannylation.[275] The compound also decomposed within two weeks when stored at 5 °C under argon to several unidentified compounds. Stannane **3.27** was therefore prepared immediately before Stille coupling experiments, and the majority of the material was stored as the stable, diastereomerically pure alcohol **3.92**.

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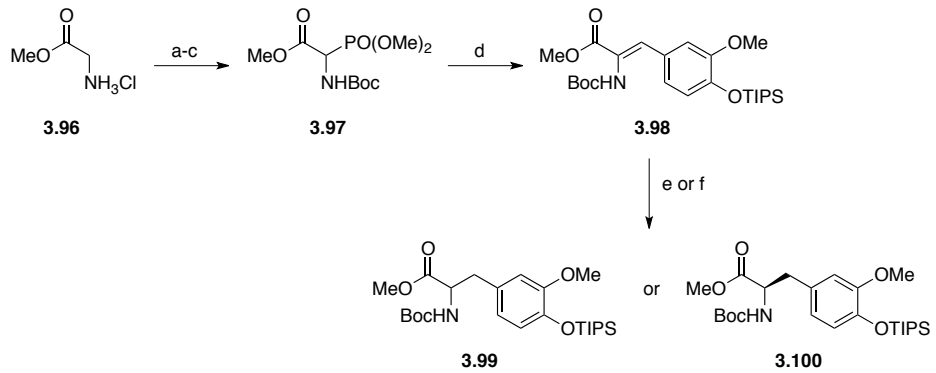
[273] R. S. Cahn, Sr. C. Ingold, V. Prelog, *Angew. Chem. Int. Ed.* **1966**, *4*, 385.
[274] J. -F. Betzer, F. Delaloge, B. Muller, A. Pancrazi, J. Prunet, *J. Org. Chem.* **1997**, *62*, 7768; J. R. Frost, C. M. Pearson, T. M. Snaddon, R. A. Booth, S. V. Ley, *Angew. Chem. Int. Ed.* **2012**, *51*, 9366.
[275] J. C. Cochran, S. C. Bayer, J. T. Bilbo, M. S. Brown, L. B. Colen, F. J. Gaspirini, D. W. Goldsmith, M. D. Jamin, K. A. Nealy, *Organometallics* **1982**, *1*, 586.

In summary, stannane fragment **3.27** was expediently synthesized in six steps in an overall yield of 42% starting from *R*-mandelic acid (**3.82**) with four chromatographic purifications on a multigram scale.

### 3.7.3 Synthesis of the Dipeptide Fragment

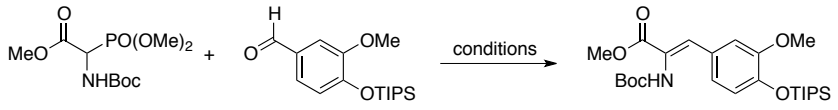



**Scheme 3.24**: Synthesis of the protected α-amino acid **3.100**. a) $Boc_2O$, $NaHCO_3$, NaCl, $CHCl_3$, $H_2O$, reflux, 2 h, 96%; b) AIBN, NBS, hν, $CCl_4$, reflux, 2 h; c) $P(OMe)_3$, DCM, reflux, 18 h, 60% over two steps; d) DBU, 3-methoxy-4-[(triisopropylsilyl)oxy]-benzaldehyde, DCM, 0 °C to r.t., 1 h, 69%, *E*/*Z*>30:1; e) $H_2$, Pd/C, MeOH, r.t., 18 h, 40%; f) $H_2$, (*R*,*R*)-Et-Duphos-Rh (I) triflate, EtOAc, r.t., 3–5 d, 98%, 98:2 e.r.

The last challenge to be addressed was the synthesis of the dipeptide fragment **3.26**. Initially, the phosphonate **3.97** was prepared in a three-step sequence according to a literature procedure (Scheme 3.24).[276] Commercially available methyl glycinate hydrochloride (**3.96**) was protected with Boc-anhydride in the presence of sodium bicarbonate in a biphasic reaction to give the product in 96% yield after aqueous workup. The Boc-protected product was then subjected to radical bromination (AIBN, NBS, hν, $CCl_4$), and the obtained labile bromide directly underwent an Arbuzov reaction with trimethyl phosphite to give the phosphonate **3.97** in 60% yield over two steps. We then commenced screening for optimal HWE conditions to form the *Z*-enamide **3.98**, as summarized in Table 3.6.

[276] J. Fischer, H. Ritter, *Beilstein J. Org. Chem.* **2013**, *9*, 2803; T. Nakajima, K. Nakayama, I. Shimizu, *J. Label. Compd. Radiopharm.* **2007**, *50,* 622.

**Table 3.6**: Screening of HWE reaction conditions to give enamide **3.98**.




3.97 3.101 3.98

| Entry | 3.1.02 (eq.) | 3.1.06 (eq.) | Base (eq.) | Solvent | Time | Yield |
|---|---|---|---|---|---|---|
| 1 | 1.00 | 1.10 | TMG (1.10) | DCM | 2 h | 25% |
| 2 | 1.00 | 1.10 | TMG (1.10) | THF | 2 h | 25% |
| 3 | 1.00 | 1.10 | DBU (1.10) | DCM | 1 h | 26% |
| 4 | 1.00 | 1.10 | DBU (1.10) | THF | 1 h | 24% |
| 5 | 1.50 | 1.00 | DBU (1.50) | DCM | 1 h | 40% |
| 6 | 1.50 | 1.00 | DBU (1.10) | DCM | 1 h | 45% |
| 7 | 1.00 | 2.00 | DBU (1.05) | DCM | 1 h | 65% |

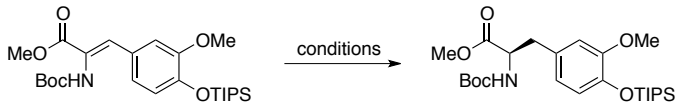
TMG: tetramethyl guanidine; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene.

This type of HWE reaction has been carried out on very similar substrates to give aromatic *Z*-enamides for subsequent enantioselective hydrogenation. The reported conditions usually utilize DBU or TMG as the base in THF or DCM and are often very high yielding (≥90%).[277] Therefore, it was unexpected when initial experiments applying these standard conditions (entries 1 to 4) gave low yields of about 25%. We also observed considerable side-product formation and could identify TIPS-deprotection as the main cause of the erosion in yield. Although reportedly being one of the most stable silyl ether protecting groups for phenols,[278] we found one literature example of a HWE reaction with a TIPS-protected phenol also with lower yields (71%).[279] While shortening the reaction time (entries 5 and 6) already proved to be beneficial, the final conditions involved careful reaction monitoring of the reaction by TLC in order to immediately observe excessive side product formation (usually after 1 hour) and employing an excess of the aldehyde **3.101** and a minimal excess of DBU (entry 7). These conditions gave the desired *Z*-enamide **3.98** in an acceptable yield of 65%.

[277] S. P. Roche, S. Faure, *Angew. Chem. Int. Ed.* **2008**, *47*, 6840; H. Chen, J.-P. Luzy, N. Gresh, C. Garbay, *Eur. J. Org. Chem.* **2006**, 2329; J. M. Travins, F. A. Etzkorn, *J. Org. Chem.* **1997**, *62*, 8387.
[278] N. Shimizu, N. Takesue, S. Yasuhara, T. Inazu, *Chem. Lett*. **1993**, 1807.
[279] S. P. Roche, S. Faure, D. J. Aitken, *Angew. Chem. Int. Ed.* **2008**, *47*, 6840.

We then prepared the racemic reference compound **3.1.04** by hydrogenation with palladium on activated charcoal and commenced screening of asymmetric hydrogenation conditions to form amide **3.100** (Table 3.7).

**Table 3.7**: Screening of asymmetric hydrogenation conditions of enamide **3.98**.




**3.98** **3.100**

| Entry | Temperature | Solvent | Conversion | Yield | e.r. |
|---|---|---|---|---|---|
| 1 | r.t. | MeOH | 80% | – | – |
| 2 | r.t. | MeOH/DCM | quant. | 95% | 99:1 |
| 3 | r.t. | EtOAc | quant. | 95% | 98:2 |
| 4 | 38 °C | MeOH | quant. | 85% | 96:4 |
| 5 | 38 °C | MeOH/DCM | quant. | 95% | 98:2 |
| 6 | 38 °C | EtOAc | quant. | 97% | 98:2 |

General conditions: $H_2$ (7.5 bar), (*R*,*R*)-Et-Duphos-Rh(I) triflate (0.5 mol%), 0.3 M.

All reactions were conducted in the presence of the catalyst (*R*,*R*)-Et-Duphos-Rh(I) triflate (0.5 mol%).[280] This catalyst is one of the pinnacles of many years of evolution of chiral (bidentate-) phosphine ligands originally developed by Nobel laureate William Standish Knowles, and its usefulness was impressively demonstrated in the Monsanto L-Dopa process.[281] Duphos-type ligands have found wide application in the preparation of chiral unnatural amino in total synthesis.[282] An initial solvent screening at 7.5 bar of $H_2$ pressure revealed pure methanol (entry 1) to be inferior to a mixture of methanol and DCM or pure ethyl acetate (entries 2 and 3). In order to increase the reaction rate and assure complete conversion, we performed the same reactions at elevated temperatures and also observed excellent yields and enantiomeric ratios (entries 4 to 6).

[280] M. J. Burk, M. F. Gross, G. P. Harper, C. S. Kalberg, J. R. Lee, J. P. Martinez, *Pure Appl. Chem*. **1996**, *68*, 37.
[281] Selected review articles: W. S. Knowles, *Angew. Chem. Int. Ed*. **2002**, *41*, 1998; P. Y. Yoon, E. N. E. E. Jacobsen, *Science*, **2003**, *299*, 1691; T. P. Dang, H. P. Kagan, *J. Chem. Soc. Chem. Commun*. **1971**, 481; R. Noyori, *Adv. Synth. Catal.* **2003**, *1*, 15.
[282] K. C. Nicolaou, F. Murphy, S. Barluenga, T. Ohshima, H. Wei, J. Xu, D. L. F. Gray, O. Baudoin, *J. Am. Chem. Soc.* **2000**, *122*, 3830; M. Toumi, F. Couty, G. Evano, *J. Org. Chem*. **2007**, *72*, 9003; A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 3552; C. Chan, R. Heid, S. Zheng, J. Guo, B. Zhou, T.Furuuchi, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 4596.

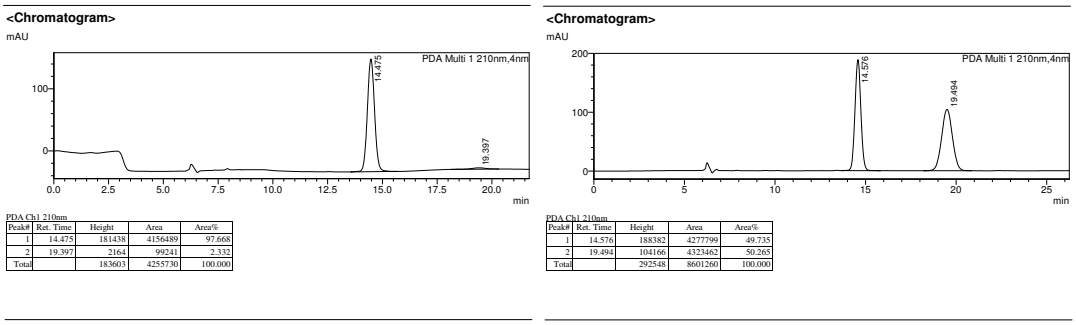
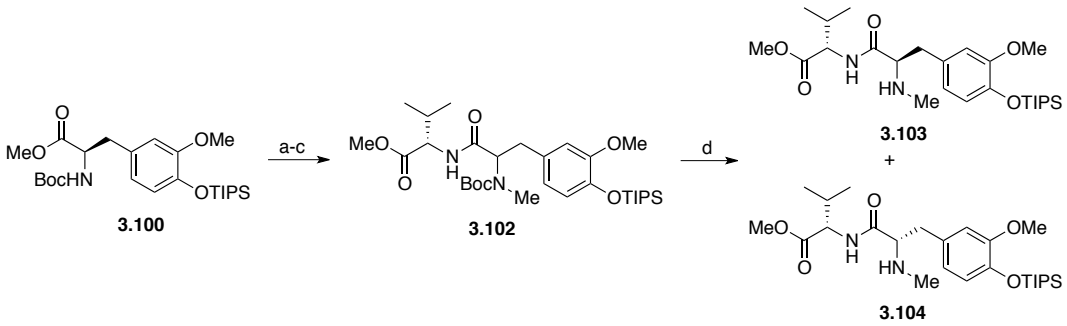



**Figure 3.12**: Comparison of the chiral HPLC trace of enantiopure compound **3.100** (left) and the racemic compound **3.99** (right).

Although entry 6 reports an inferior e.r. of 98:2 compared to entry 2 (99:1), this difference probably lies well within the standard deviation at the detection limit. The chiral HPLC traces of **3.99** and **3.100** are shown in Figure 3.12.

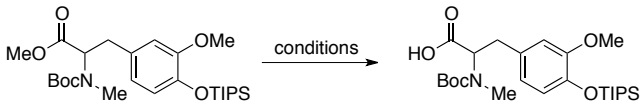
We then continued the synthesis of the dipeptide fragment **3.26** as outlined in Scheme 3.25. The initial methylation of the chiral carbamate **3.100** with methyl iodide is well documented in the literature for similar substrates to give enantiopure products.[282] Unfortunately, complete racemization occurred under these basic conditions, but we were not able to identify this issue until a later stage. The resulting complications are reported in the following sections.




**Scheme 3.25**: Synthesis of the diastereomeric dipeptides **3.103** and **3.104**. a) NaH, MeI, DMF, r.t., 2 h, 93%; b) NaOH, THF/MeOH/water, r.t., 2 h, 78%; HBTU, HOBT, DIPEA, DCM, 0 °C to r.t., 18 h, 81%; d) TFA, DCM, r.t., 30 min, quant., **3.103**/**3.104** 1:1.

The methylation in DMF gave 91% yield and a 5:4 mixture of rotamers was observed. Again formation of byproducts was observed, presumably due to TIPS-deprotection. The saponification of the methyl ester **3.1.10** to give the free acid **3.1.11** was then thoroughly investigated (Table 3.8).

**Table 3.8**: Screening of saponification conditions of ester **3.105**.




3.105 3.106

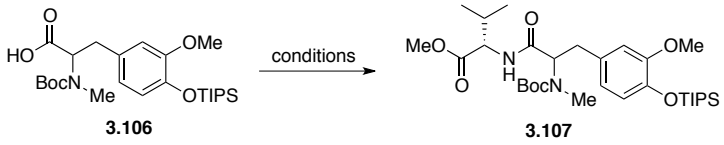
| Entry | Base (eq.) | Time | Yield[a] |
|---|---|---|---|
| 1 | LiOH (2.0) | 16 h | 22% |
| 2 | KOH (2.0) | 30 min | 45% |
| 3 | KOH (1.0) | 30 min | 44% |
| 4 | NaOH (2.0) | 16 h | 46% |
| 5 | NaOH (2.0) | 1 h | 65% |
| 6 | NaOH (1.5) | 2 h | 78% |

General conditions: THF/MeOH/$H_2O$ 3:1:1, 0.2 M, r.t. a) after chromatographic purification.

Initial experiments employing standard conditions gave very low yields (entry 1). We also observed TIPS-deprotected side product. When stronger bases were used, the yield increased but so did side product formation (entries 2 and 3). However, shorter reaction times clearly proved to be beneficial (entries 5 and 6). We then settled for sodium hydroxide at a slight excess of 1.5 equivalents and two hours reaction time, giving the acid in 78% yield after column chromatography (entry 6). This was later further improved for the enantiopure amino ester **3.111**. Chromatographic purification also proved to be mandatory, as the formed byproducts greatly decreased the yield of the following peptide coupling reaction.

The results of the investigation of the peptide bond formation of acid **1.106** are summarized in Table 3.9. Initially, the suitability of phosphonium-, carbodiimide- and uronium based coupling reagents was investigated (entries 1-3). HBTU (entry 1) and PyBOP (entry 3) both gave satisfactory yields. Next, the influence of the solvent was investigated. A slight decrease in yield when the solvent was changed to THF (entry 4), however this could be overcome by starting the reaction at 0 °C and gradually warming to room temperature (entry 5).

**Table 3.9**: Screening of peptide coupling conditions to form dipeptide **3.107**.




**3.106** **3.107**

| Entry | Solvent | Temp. | Reagent (eq.) | Yield |
|---|---|---|---|---|
| 1 | DMF | r.t. | HBTU (1.1) | 67% |
| 2 | DMF | r.t. | EDC (1.2), HOBt (1.2) | 20% |
| 3 | DMF | r.t. | PyBOP (1.2) | 64% |
| 4 | THF | r.t. | HBTU (1.1) | 57% |
| 5 | THF | 0 °C to r.t. | HBTU (1.1) | 65% |
| 6 | DCM | r.t. | HBTU (1.1) | 34% |
| 7 | DCM | 0 °C to r.t. | HBTU (1.1), HOBt (1.1) | 81% |

General conditions: methyl valinate hydrochloride (1.0 eq.), DIPEA (2.2 eq.), 0.3 M.

DCM initially proved to be a poor solvent (entry 6), but addition of HOBt and increasing temperature gave a good yield of 81% (entry 7).

This was also the first stage where we observed some irregularities in the 1H NMR spectrum, e.g. two sets of signals for some peaks in a 1:1 ratio. We suspected a combination of peptide- and carbamate rotamers to be responsible for this observation. We tried to prove this by measuring high temperature NMR spectra to confirm the expected coalescence of the signals (Figure 3.13).

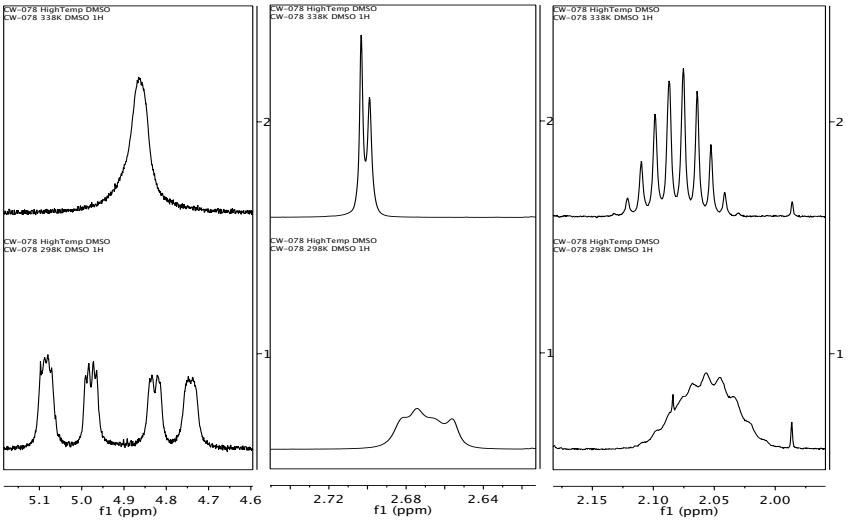



**Figure 3.13**: $^{1}$H NMR spectra of compound **3.107** at 298 K (lower spectrum) and 338 K (upper spectrum) in DMSO.

From these experiments, we found signal of the valine proton with two vicinal methyl groups at 2.05 ppm clearly to coalescence to a much sharper signal. The same effect was observed for the valine α-proton at 4.7 ppm, although a rather broad signal was still observed. The *N*-methyl group at 2.7 ppm still showed a distinct set of two signals, even though the peaks were much sharper than at the lower temperature, indicating some coalescence. These ambiguous findings did not clarify whether the compound only was in an equilibrium of rotamers, or if it was indeed a diastereomeric mixture. We therefore continued with the Boc deprotection with TFA in DCM, which gave the partially separable diastereomeric dipeptides **3.103** and **3.104** as a 1:1 mixture in quantitative yield (Scheme 3.25).

**Table 3.10**: Screening of Boc deprotection conditions of **3.107**.

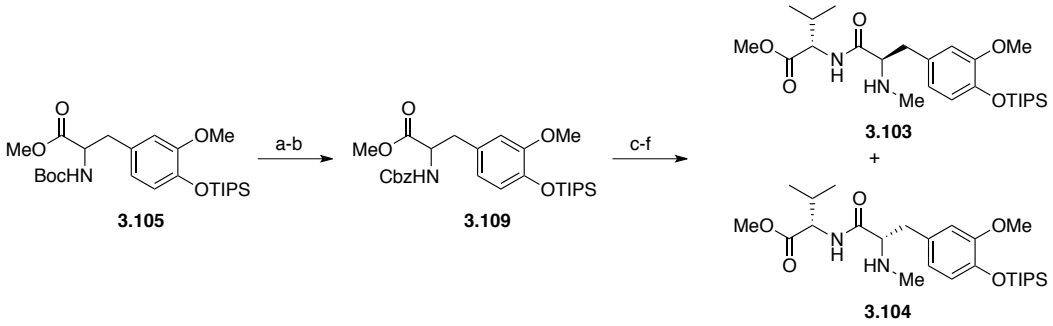

**3.107** **3.108**

| Entry | Conditions | Temperature | Time | 3.103:3.104[a] |
|---|---|---|---|---|
| 1 | DCM/TFA 3:2 | r.t. | 1 h | 1:1 |
| 2 | HCl (1M in $Et_2O$) | r.t. | 14 h | No Conversion |
| 3 | DCM/TFA 4:1 | r.t. | 1 h | 1:1 |
| 4 | HCl (4M in dioxane) | 85 °C | 1 h | 1:1 |
| 5 | $H_3PO_4$/DCM 1:1 | r.t. | 72 h | 1:1 |
| 6 | TFA/DCM 1:1 | 0 °C | 1 h | 1:1 |
| 7 | HCl (1M in $Et_2O$) | 40 °C | 4 h | 1:1 |
| 8 | $BiCl_3$, DCM | r.t. | 14 h | 1:1 |
| 9 | CAN, MeCN | r.t. to 60 °C | 72 h | No Conversion |

a) determined by TLC and $^1$H NMR of the crude product.

We then had to investigate in which step of the sequence (methylation, hydrolysis, peptide coupling or Boc-deprotection) racemization had occurred. Racemization

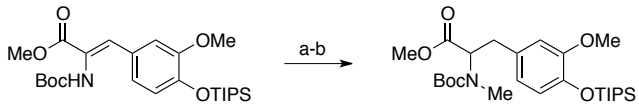
processes for methylation, coupling and Boc-deprotection reactions are known,[283] and since we had already synthesized a considerable amount of diastereomerically impure dipeptide **3.108**, we continued to screen for alternative Boc-deprotection procedures (Table 3.10). All attempts to cleave the Boc group using acidic conditions gave a diastereomeric mixture of compounds (entries 1–7). The attempts to cleave the Boc group under Lewis acidic conditions (entry 8)[284] or oxidative conditions (entry 9)[285] also proved to be futile.




**Scheme 3.26**: Synthesis of the Cbz protected amide **3.109**. a) TFA, DCM, r.t. 30 min, quant; b) CbzCl, $Na_2CO_3$, $Et_2O/H_2O$, r.t., 14 h, 96%; c) NaH, MeI, DMF, r.t., 2hh, 83%; d) NaOH, THF/MeOH/$H_2O$, r.t., 2 h; e) HBTU, HOBT, DIPEA, DCM, 0 °C to r.t., 18 h, 54% over two steps; f) $H_2$, Pd/C, MeOH, r.t., 30 min, quant., **3.103**:**3.104** 1:1.

We therefore decided to replace the Boc group by Cbz in order to clarify the issue (Scheme 3.26). The synthesis of **3.109** proceeded in a similar fashion as with the Boc protected derivative. Upon removal of the Cbz group by hydrogenation, a 1:1 mixture of the diastereomeric dipeptides **3.103** and **3.104** were obtained. We then decided to reinvestigate the sequence for indications of racemization from the beginning, starting with the methylation reaction.

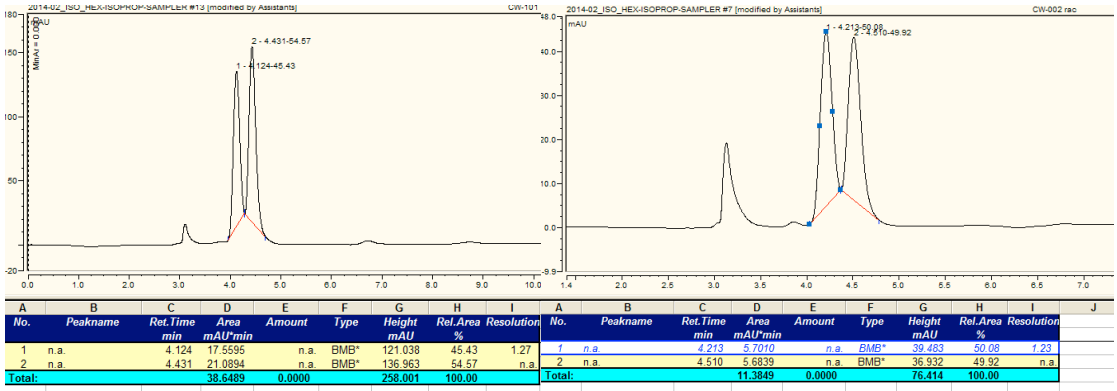
[283] S. Balakrishnan, C. Zhao, N. J. Zondlo, *J. Org. Chem.* **2007**, *72*, 9834; Y. Jiang, Z. Zhang, R. S. Di Paola, L. Hu, *Tetrahedron* **2007**, *63*, 10637; M. J. Niphakis, B. J. Turunen, G. I. Georg, *J. Org. Chem.* **2010**, *75*, 6793.
[284] R. S. Navath, K. B. Pabbisetty, L. Hu, *Tetrahedron Lett.* **2006**, *47*, 389.
[285] J. Ru Hwu, M. L. Jain, F. Y. Tsai, A. Balakumar, G. Hakimelahi, S. C. Tsay, *ARKIVOC* **2002**, *9*, 28.




**3.98** **3.110**

**Scheme 3.27**: Synthesis of the racemate **3.110**. a) $H_2$, Pd/C, MeOH, r.t., 30 min; b) NaH, MeI, DMF, r.t., 2 h, 35% over two steps.

We prepared the racemic compound **3.110** (Scheme 3.27) and developed chiral HPLC conditions to separate the enantiomers and compared it with the methylated product **3.105** synthesized from enantiopure carbamate **3.100**. Both chiral HPLC traces indicated that racemization had occurred (Figure 3.14). Thus, we had now found the cause of racemization as the carbamate methylation using sodium hydride.

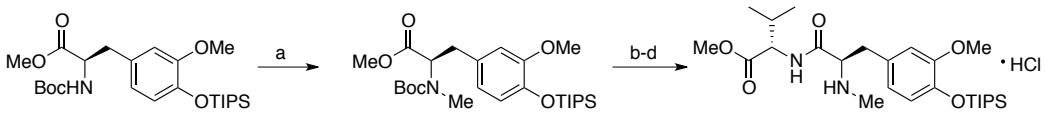



| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | n.a. | 4.124 | 17.5595 | n.a. | BMB* | 121.038 | 45.43 | 1.27 |
| 2 | n.a. | 4.431 | 21.0894 | n.a. | BMB* | 136.963 | 54.57 | n.a. |
| Total: | | | 38.6489 | 0.0000 | | 258.001 | 100.00 | |

| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | n.a. | 4.213 | 5.7010 | n.a. | BMB* | 39.483 | 50.08 | 1.23 |
| 2 | n.a. | 4.510 | 5.6839 | n.a. | BMB* | 36.932 | 49.92 | n.a. |
| Total: | | | 11.3849 | 0.0000 | | 76.414 | 100.00 | |

**Figure 3.14**: Chiral HPLC traces of the methylated product **3.1.10** (left, obtained from enantiopure hydrogenation product **3.1.05**) and the racemate **3.1.14** (right).

We then changed our methylation procedure to obtain diastereo- and enantiomerically pure material as outlined in Scheme 3.28. Methylation with methyl iodide in the presence of an excess of silver(I) oxide is another widely applied procedure for the methylation of Boc protected amines.[286] When applied to our substrate **3.100**, we were delighted to obtain the methylated carbamate **3.111** with an enantiomeric ratio of 98:2 (Figure 3.15), therefore successfully resolving the issue of racemization.



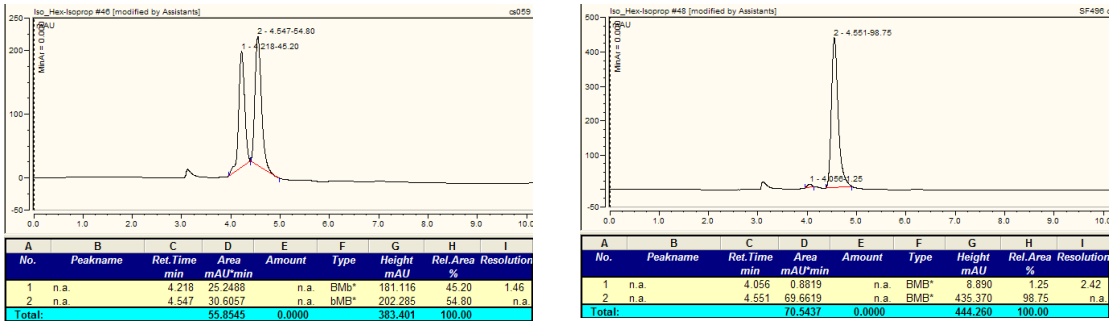

**3.100** **3.111** **3.112**

**Scheme 3.28**: Synthesis of optically pure dipeptide salt **3.112**. a) MeI, $Ag_2O$, DMF, r.t., 18 h, 97% b) NaOH, THF/MeOH/$H_2O$, r.t., 2 h; e) HBTU, HOBT, DIPEA, DCM, 0 °C to r.t., 18 h, 78% over two steps; d) HCl in dioxane (4M), r.t., 40 min, quant.

[286] L. Aurelio, R. T. C. Brownlee, A. B. Hughes, *Chem. Rev.* **2004**, *104*, 5823.

It should be noted that the silver(I) oxide must be freshly prepared prior to reaction, as an older reagent bottle gave low conversion (20%) under identical conditions. Other silver sources (e.g. silver(I) triflate, silver(I) trifluoroacetate) were also investigated, but did not yield any product. Continuing the synthesis according to our optimized route, we obtained the diastereomerically pure dipeptide fragment **3.112**.

In summary, the dipeptide fragment **3.112** was synthesized from commercially available methyl glycinate hydrochloride **3.96** in 9 steps and 29% overall yield with an enantiomeric ratio of 98:2 on a multigram scale. The main challenge was to identify the cause of racemization, which was found to be the methylation with sodium hydride and methyl iodide. This was then circumvented by methylation with methyl iodide and freshly prepared silver(I) oxide. The phenolic TIPS group also proved to be rather labile, especially under basic conditions.




| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | n.a. | 4.218 | 25.2488 | n.a. | BMb* | 181.116 | 45.20 | 1.46 |
| 2 | n.a. | 4.547 | 30.6057 | n.a. | bMB* | 202.285 | 54.80 | n.a. |
| Total: | | | 55.8545 | 0.0000 | | 383.401 | 100.00 | |

| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | n.a. | 4.056 | 0.8819 | n.a. | BMB* | 8.890 | 1.25 | 2.42 |
| 2 | n.a. | 4.551 | 69.6619 | n.a. | BMB* | 435.370 | 98.75 | n.a. |
| Total: | | | 70.5437 | 0.0000 | | 444.260 | 100.00 | |

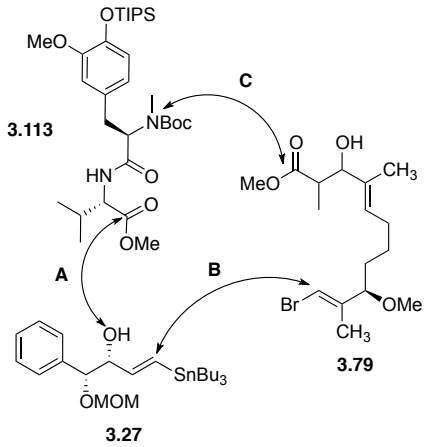
**Figure 3.15:** Chiral HPLC traces of the racemate **3.110** (left) and enantiopure compound **3.111** (right).

This reactivity was also observed later in the synthesis. With all the fragments **3.112**, **3.27** and **3.79** in hand, we proceeded with the final assembly of the macrocycle as discussed in the next section.

### 3.7.4 Synthesis of the Macrocyle

#### *3.7.4.1 Evaluation of Synthetic Routes*

We now want to the recapitulate the possible routes for assembly of the macrocycle. Scheme 3.29 outlines the main connection points and the corresponding applicable reactions. First, the inherent reactivities of the fragments are summarized.




**Scheme 3.29**: Major connections in the assembly of the macrocycle. A) esterification; B) Stille coupling; C) amide coupling.

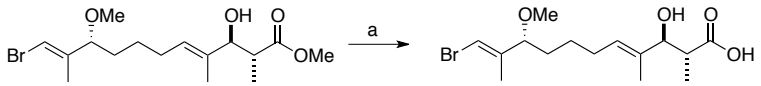
The vinyl bromide **3.79** proved to be stable under very basic conditions (aldol addition) and should also be stable under reasonably acidic conditions. In any case, the free hydroxyl group could still be protected if needed. The Boc-protected dipeptide **3.113** proved to be stable under very acidic conditions (Boc deprotection), but the TIPS group was labile under basic conditions (i.e.: ester hydrolysis, methylation with NaH). However, the lability in basic media could be harnessed by careful reaction optimization and monitoring. The vinyl stannane **3.27** was the most labile of the three fragments, as it decomposed readily at 5 °C. It would certainly degrade to some extent under acidic (MOM cleavage and protodestannylation) or basic conditions. The general reaction pathways A-C were hypothesized to consist of the following steps: A) ester hydrolysis (basic conditions), esterification (basic conditions); B) Stille coupling (neutral to basic conditions) and C) Boc deprotection (acidic conditions), ester hydrolysis (basic conditions) and peptide coupling (basic conditions). With this general framework established, we now considered all possible reaction sequences and evaluated their likeliness to cause decomposition or side reactions based on the known properties of the compounds described before. Table 3.11 illustrates that three sequences A-B-C, A-C-B and B-A-C could be immediately ruled out. They all contained the Boc deprotection in presence of the MOM ether or the vinyl stannane. These functional groups would most likely decompose under these harsh conditions.

**Table 3.11**: Evaluation of reaction sequences.

| Sequence | Considerations |
|---|---|
| A-B-C | Boc deprotection in presence of MOM |
| A-C-B | Boc deprotection in presence of MOM and stannane |
| B-C-A | Chemoselectivity between –NH and –OH groups in peptide coupling and esterification |
| B-A-C | Boc deprotection in presence of MOM and allylic alcohol |
| C-A-B | Positional selectivity between two –OH group in esterification |
| C-B-A | Positional selectivity between two –OH group in esterification |

The anticipated problems for the sequences B-C-A, C-A-B and C-B-A mainly consisted of possible chemoselectivity issues for the differentiation between a secondary amine and a hydroxy group in the peptide coupling reaction (sequence B-C-A) or positional selectivity issues between two hydroxy groups in the esterification (sequences C-A-B and C-B-A). For the last two sequences, these positional selectivity issues, should they be observed, could be solved with a simple protection of the allylic alcohol. We then chose to investigate the sequences C-A-B and C-B-A.

*3.7.4.2 Assembly of the Fragments*

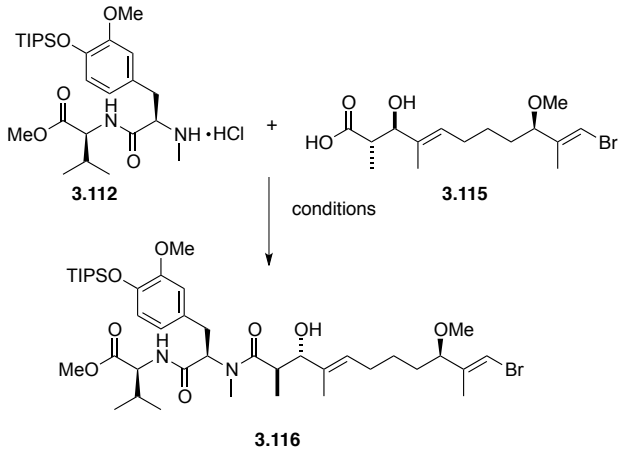



**3.114** **3.115**

**Scheme 3.30**: Hydrolysis of ester **3.114**: a) NaOH, THF/MeOH/$H_2O$, r.t., 2 h, quant.

We first investigated the peptide coupling reaction between the acid **3.115** and secondary amine **3.112** as the initial step. First, the chromatographically separated *anti*-configured ester **3.114** was hydrolyzed with sodium hydroxide in a mixture of THF/MeOH/$H_2O$ in quantitative yield (Scheme 3.30). The crude acid was then directly subjected to the peptide coupling conditions, and our screening efforts for this reaction are summarized in Table 3.12.

**Table 3.12**: Screening of peptide coupling conditions to give peptide **3.116**.



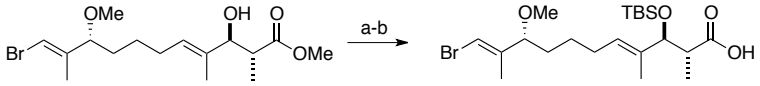

| Entry | Reagent (eq.) | 3.112 (eq.) | 3.115 (eq.) | Yield |
|---|---|---|---|---|
| 1 | HBTU (1.4), HOBt (2.0) | 2.0 | 1.0 | 0% |
| 2 | PyBroP (1.1) | 1.8 | 1.0 | 0% |
| 3 | DMTMM-Chloride (1.5) | 1.5 | 1.0 | 0% |
| 4 | DMTMM-$BF_4$ (1.5) | 1.2 | 1.0 | 0% |
| 5 | T3P (1.5) | 1.2 | 1.0 | 0% |
| 6 | EDC (2.0) | 1.2 | 1.0 | 0% |

General conditions: $NEt_3$ (3.0 eq.), DCM, 0.15 M, 0 °C to r.t.. T3P: 1-Propanephosphonic anhydride solution.

We anticipated the peptide coupling to be challenging, since both the acid **3.115** and the secondary amine **3.112** are sterically very hindered. Several very reactive coupling reagents for difficult peptide bond formations have been developed in recent years,[287] and we focused on the reportedly most efficient reagents. We started our screening with an excess of amine in order to push the reaction to completion (entry 1 to 3), but since we did not observe any conversion, we lowered the amount of amine to 1.2 equivalents for the following reactions. We first used our previously described procedure involving uronium-based reagent HBTU and HOBt (entry 1), but without success. We then tried to apply phosphonium based reagent PyBroP,[288] which also did not give the desired

[287] Reviews: C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827; M. Joullié, K. M. Lassen, *ARKIVOC* **2010**, *8*, 189.
[288] E. Frerot, J. Coste, A. Pantaloni, M.-N. Dufour, P. Jouin, *Tetrahedron* **1991**, *47*, 259.

product (entry 2). Triazinylammonium salts[289] (entries 3 and 4), the phosphonic anhydride based reagent T3P[290] (entry 5) and EDC (entry 6) also yielded no product. It should be noted that for all these reactions, we were able to reisolate considerable amount of the free amine of **3.112**, indicating that the amine indeed was not very nucleophilic or that no active ester was formed in the first place. We also did not observe any homocoupling of the acid with the allylic alcohol, which might also be due to insufficient amounts of active ester formed, or the sterically hindred acid **3.115**. In analogy to the synthesis reported by Ghosh and co-workers,[221] we then synthesized the TBS-protected acid **3.117** (Scheme 3.31).



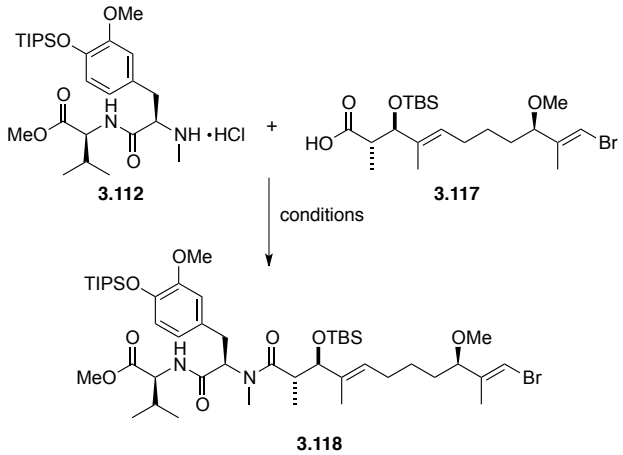

**3.114** **3.117**

**Scheme 3.31**: Synthesis of acid **3.117**: a) TBSOTf, 2,6-lutidine, 0 °C to r.t., 20 min, 80%; b) KOH, THF/MeOH/$H_2O$, 80 °C, microwave, 18 h, quant.

The TBS-group on the *anti*-diastereomer **3.114** was introduced with TBS triflate in presence of 2,6-lutidine in good yield. Initial experiments under our standard methyl ester hydrolysis conditions (NaOH, THF/MeOH/$H_2O$, r.t.) showed low conversion (10%) after 18 hours reaction time for the subsequent hydrolysis. We suspected the increased steric bulk introduced by the TBS-group to be responsible for this. Thus, we applied more forcing conditions with potassium hydroxide as a base in a biphasic mixture with THF and water at 80 °C for 18h hours in a microwave reactor. This furnished free acid **3.117** in quantitative yield and no epimerization was observed. We then continued with the screening of peptide coupling conditions as presented in Table 3.13. The observed results were very similar to those reported in Table 3.12, and none of the peptide coupling reagents gave a trace of product (entries 1 to 6). In the case of EDC in the presence of HOBt, we were even able to isolate the HOBt ester formed with acid **3.117** by flash chromatography (entry 3). This result underlined the weak nucleophilic character of the secondary amine, but also the great steric hindrance induced by the TBS group, which was in line with the observation of the preceding hydrolysis reaction.

[289] Z. J. Kamiński, B. Kolesińska, J. Kolesińska, G. Sabatino, M. Chelli, P. Rovero, M. Błaszczyk, M. L. Główka, A. M. Papini, *J. Am. Chem. Soc.* **2005**, *127*, 16912.
[290] T. Vishwanatha, N. Panguluri, V. Sureshbabu, P. Vasavaprabhu, *Synthesis* **2013**, *45*, 1569.

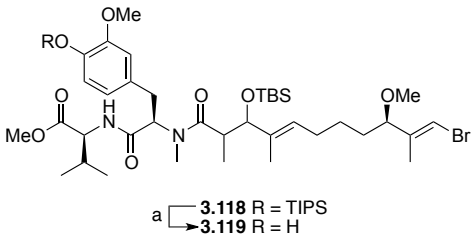
**Table 3.13**: Screening of peptide coupling conditions to form peptide **3.118**.




| Entry | Reagent (eq.) | 3.112 (eq.) | 3.117 (eq.) | Yield |
|---|---|---|---|---|
| 1 | HBTU (1.4), HOBt (2.0) | 1.0 | 1.0 | 0% |
| 2 | T3P (1.5) | 1.0 | 1.0 | 0% |
| 3 | EDC (2.0), HOBt (2.0) | 1.0 | 1.0 | 0% |
| 4 | PyBroP (2.0) | 1.0 | 1.0 | 0% |
| 5 | DMTMM-Chloride (2.0) | 1.0 | 1.0 | 0% |
| 6 | DMTMM-$BF_4$ (2.0) | 1.0 | 1.0 | 0% |
| 7 | $(ClCO)_2$ (20), DMAP (0.1) | 1.0 | 1.2 | 51% |

General conditions: $NEt_3$ (3.0 eq.), DCM, 0.15 M, 0 °C to r.t.

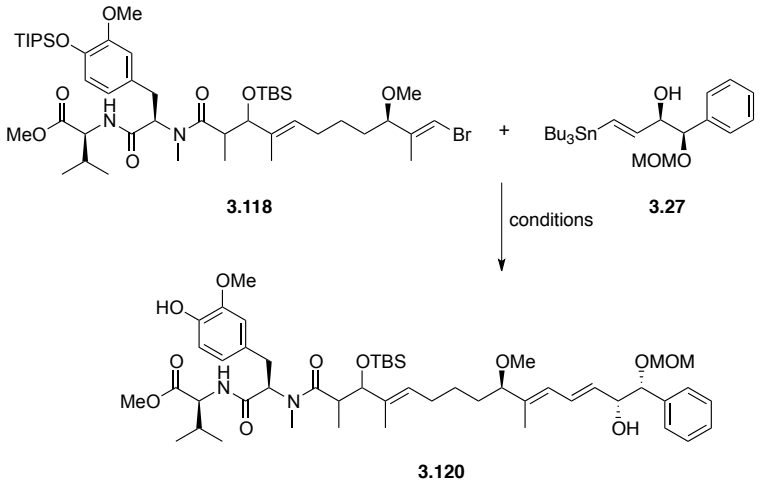
Our last resort was the formation of an acyl halide as a very electrophilic species and trapping it with the amine **3.112** to afford the desired product **3.118** in 51 % yield. This was accompanied by complete epimerization at the α-position of the acid, giving an inseparable mixture 1:1 *syn*:*anti* mixture of diastereomers. We also suspected the hydrochloric acid already present in the oxalyl chloride and inevitably formed during the reaction lowered the yield by cleaving the TBS group as a side reaction. We tried to selectively remove the TBS group with one equivalent of TBAF and then oxidize to the enone, but instead we selectively removed the phenolic TIPS group (Scheme 3.32), although the TBS group was expected to be cleaved first.




**Scheme 3.32**: Selective TIPS deprotection of **3.118**. a) TBAF, THF, r.t., 1 h, 78%.

However, there have been reports on selective TBSOR (R = aliphatic) deprotections in presence of TBSOAr and *vice versa*.[291] Nevertheless, with the two fragments finally coupled, we continued with the investigation of the Stille reaction (Table 3.14).

**Table 3.14**: Screening of Stille coupling conditions to form diene **3.120**.

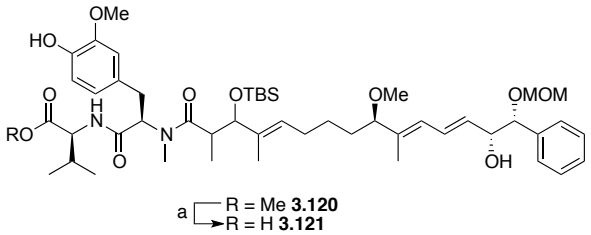



| Entry | Reagents (eq.) | Observations | Yield |
|---|---|---|---|
| 1 | $Pd(MeCN)_2Cl_2$ (1.0) | No conversion | 0% |
| 2 | $Pd(PtBu_3)_2$ (1.0) | Only **3.27** consumed | 0% |
| 3 | $Pd(PPh_3)_4$ (1.0) | Only **3.27** consumed | 0% |
| 4 | $NBu_4Ph_2PO_2$ (4.0), CuTC (2.0) | Only **3.27** consumed | 0% |
| 5 | $Pd(PPh_3)_4$ (1.0), $NBu_4Ph_2PO_2$ (4.0), CuTC (2.0) | **3.118** and **3.27** consumed | 33% |
| 6 | $Pd(PPh_3)_4$ (1.0), $NBu_4Ph_2PO_2$ (4.0), CuTC (3.5) | **3.118** and **3.27** consumed | 63% |

General conditions: **3.27** (1.2 eq.), **3.1.22** (1.0 eq.) DMF (degassed), 0.1 M, 70 °C, 18 h.

[291] E. W. Collington, H. Finch, I. J. Smith, *Tetrahedron Lett*. **1985**, *26*, 681.

Standard conditions[292] employing bis(acetonitrile)palladium(II) chloride as the pre-catalyst proved to be ineffective for this reaction, as no conversion was observed (entry 1). When different palladium(0) catalysts were used, consumption of the stannane **3.27** was observed, but the bromide **3.118** remained untouched (entries 2 and 3). This observation might indicate a faster stannane homocoupling than the oxidative reaction of the bromide, which remains unchanged. Bromides similar to **3.118** bearing a vicinal methyl group have been shown to be a rather difficult substrate in Stille reactions, and often the vinyl iodide is preferred.[293] We therefore applied the conditions developed by Fürstner's group for "*exigent Stille-Migita reactions*",[294] where CuTc is added for a proposed transmetalation of the stannane[295] and Hedeke's salt ($NBu_4Ph_2PO_2$) acts as a tin scavenger.[296] The presence of a large excess (3.5 eq.) of the copper compound is absolutely required, as comparison of entries 4 to 6 indicates. For entries 5 and 6, the stannane **3.27** was no longer observed in TLC within 30 minutes, but the reaction had to be stirred at 70 °C for at least 12 hours for complete consumption of the bromide **3.118**.




**Scheme 3.33**: Hydrolysis of methyl ester **3.120**. a) KOH, THF/MeOH/$H_2O$, r.t., 30 min, quant.

[292] G. Pohnert, *Angew. Chem. Int. Ed*. **2000**, *39*, 4352; K. Miyashita, M. Ikejiri, H. Kawasaki, S. Maemura, T. Imanishi, *J. Am. Chem. Soc*. **2003**, *125*, 8238; S. K. Woo, E. Lee, *J. Am. Chem. Soc*. **2010**, *132*, 4564; S. K. Woo, E. Lee, *J. Am. Chem. Soc*. **2010**, *132*, 4564; T. Esumi, N. Okamoto, S. Hatakeyama, *Chem. Commun*. **2002**, 3042.

[293] I. Paterson, V. A. S. N. Doughty, M. D. McLeod, T. Trieselmann, *Tetrahedron* **2011**, *67*, 10119; R. Villa, A. L. Mandel, B. D. Jones, J. J. La Clair, M. D. Burkart, *Org. Lett*. **2012**, *14*, 5396; K. C. Nicolaou, Y.-P. Sun, R. Guduru, B. Banerji, D. Y. K. Chen, *J. Am. Chem. Soc*. **2008**, *130*, 3633.

[294] A. Fürstner, J.-A. Funel, M. Tremblay, L. C. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, *Chem. Commun.* **2008**, 2873.

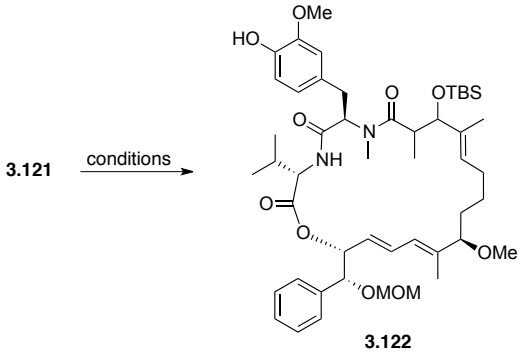
[295] L. S. Liebeskind, R. W. Fengl, *J. Org. Chem*. **1990**, *55*, 5359; V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem*. **1994**, *59*, 5905; S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed*. **2004**, *43*, 1132.

[296] J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc*. **1997**, *119*, 12376; A. B. Smith, K. P. Minbiole, P. R. Verhoest, M. Schelhaas, *J. Am. Chem. Soc*. **2001**, *123*, 10942; T. B. Durham, N. Blanchard, B. M. Savall, N. A. Powel, W. R. Roush, *J. Am. Chem. Soc*. **2004**, *126*, 9307.

Surprisingly, we obtained the TIPS-deprotected product **3.120** under optimized conditions in 63 % yield, once more underlining the unexpected lability of this phenolic silyl group. We were able to partially separate the diastereomers of the β-hydroxy amide at this stage and obtained a more easily interpretable $^{1}$H NMR spectrum.

Although selective protections of phenolic hydroxyl groups in presence of aliphatic hydroxyl groups have been reported,[297] we decided to directly investigate the macrolactonization with compound **3.120** bearing the free phenolic hydroxyl group (Table 3.15). The hydrolysis of ester **3.120** proceeded under standard conditions in quantitative yield (Scheme 3.33).

**Table 3.15**: Screening of macrolactonization conditions of seco acid **3.121**.



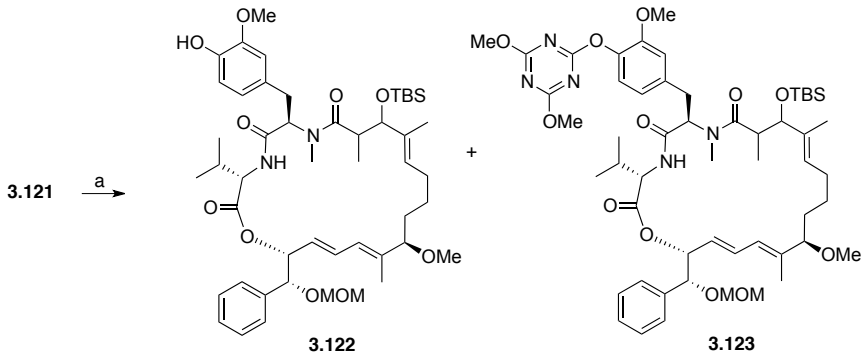

**3.122**

| Entry | Conditions (eq.) | Observations |
|---|---|---|
| 1 | EDC (1.0), DCM | Traces of **3.122** |
| 2 | TCBC (1.0), DMAP (0.1), toluene | No conversion |
| 3 | cyanuric chloride (1.0), DCM | No conversion |
| 4 | HBTU (1.0), DCM | No conversion |
| 5 | T3P (1.0), DCM | No conversion |
| 6 | DMTMM-$BF_4$ (1.0), DCM | Traces of **3.122** |
| 7 | 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.0), MeCN | Traces of **3.122** |
| 8 | DCC (1.0), DMAP (0.1), MeCN | No conversion |

a) KOH, THF/MeOH/$H_2O$, r.t., 30 min, quant; General macrolactonization conditions: DIPEA (1.0 eq.), 1 mM, r.t., 3 d.

[297] M. Sefkow, H. Kaatz, *Tetrahedron Lett.* **1990**, *40*, 6561.

Macrolactonizations have been employed in many total syntheses, and a myriad of reagents are available.[298] Indeed, many of the reagents have shown to be suitable for ester as well as amide bond formation, as both reactions usually involve the activation of a carboxylic acid. We expanded upon our array of previously applied peptide coupling reagents (entries 1, 4, 5 and 6) by using more specific macrolactonization reagents (entries 2, 3, 7 and 8). Yamaguchi-[299] and Steglich[300] conditions (entries 7 and 8) did not lead to formation of product, and neither did HBTU, T3P and DMTMM (entries 3 to 5). However, in the crude products of the triazine based reagents (entries 6 and 7) and EDC (entry 1), we were able to identify the desired product **3.122** by ESI-MS. TLC also indicated that the largest quantity of product was formed for entry 6.

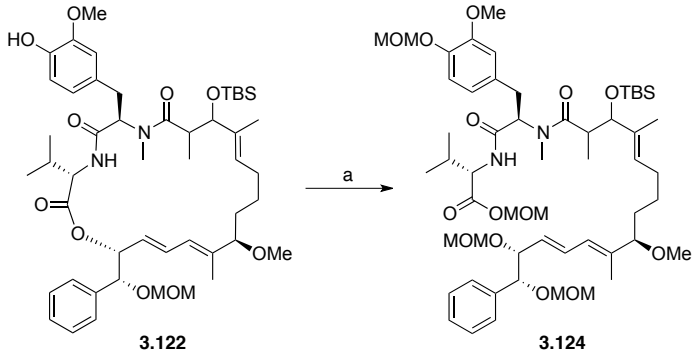



**Scheme 3.34**: Macrolactonization to form macrocycle **3.122** and **3.123**. a) DMTMM-$BF_4$, DIPEA, DCM, 0.3 mM, r.t., 4–6 d, 15%.

We performed the reaction on a larger scale (Scheme 3.34). An initial experiment with 50 mg of the acid gave 15% yield of the lactone **3.122**. In spite of a very low yield, we were encouraged by this result, as outcome of macrolactonizations are often highly substrate dependent due to macrocyclic stereocontrol.[301] A similar substrate had also been shown to be reluctant to undergo macrolactonization, as a discussion with Prof. Markus Kalesse revealed to us. Unfortunately, when the reaction was repeated on the same scale, we isolated exclusively compound **3.123** in 14% yield, resulting from an attack of the phenolic hydroxyl group on the coupling reagent. This problem might be solved by using a lower amount of DMTMM-$BF_4$ than the applied 5.0 equivalents and by performing the reaction under less basic conditions. We also noted that our ESI sample of compound **3.122** ($M+Na^+$ = 901.9) in acetonitrile decomposed almost

[298] A. Parenty, X. Moreau, G. Niel, J. M. Campagne, *Chem. Rev.* **2013**, *113*, 1.
[299] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989.
[300] B. Neises, W. Steglich, *Angew. Chem. Int. Ed*. **1978**, *17*, 522.
[301] E. M. Carreira, L. Kvaerno, *Classics in Total Synthesis*, **2008**, WILEY-VCH, Weinheim.

completely to an unknown compound with m/z = 889.9 over night. We were nevertheless able to measure an HRMS-ESI spectrum and could confirm the identity of macrolactone **3.122**.




**3.122** **3.124**

**Scheme 3.35**: Failed MOM protection of macrolactone **3.122**. a) MOMCl, DIPEA, DCM, 0 °C to r.t., 30 min, quant.

With the presumably labile lactone **3.122** in hand, we had no choice but to quickly continue the synthesis. The next step we addressed was the oxidation of the β-hydroxy amide function. We first tried to protect the free phenolic hydroxy group, as such *ortho*-methoxy phenols easily undergo *ortho*-quinone formation and other side reactions under oxidative conditions.[302] We decided to introduce another MOM group to allow for a later global deprotection in a later step (Scheme 3.35). When macrolactone **3.122** was treated with MOMCl in the presence of DIPEA in DCM, the starting material was completely consumed, but two new products were formed. Since the quantities obtained were too low to measure a $^{1}$H NMR spectrum, we had to rely on ESI-MS to identify the products. The desired product had a mass of 804.4 Da, but the two compounds we had isolated had their major m/z signals at m/z = 1027.9 and m/z = 939.9/999.0 respectively. The overly MOM protected compound **3.124** has a similar mass of m/z = 1028.6 and was suspected to be the first of our isolated compounds. However, we were not able to identify a reasonable structural formula to account for the peaks with m/z = 939.9 and m/z = 999.0. Nevertheless, we tried to TBS-deprotect the mixture of the two unknown compounds. We knew from the work of Ghosh's group that the deprotection of the TBS group would require rather forcing conditions,[221] but not even when using TBAF (1M in THF) as the solvent at 40 °C in the presence of acetic acid did we observe any

[302] D. Magdziak, A. A. Rodriguez, R. W. Van De Water, T. R. R. Pettus, *Org. Lett.* **2002**, *4*, 285; K. Virgel, N. Esguerra, Y. Fall, L. Petitjean, J.- P. Lumb, *J. Am. Chem. Soc.* **2014**, *136*, 7662. S. H. Dai, C. Y. Lin, D. V. Rao, F. A. Stuber, P. S. Carleton, H. Ulrich, *J. Org. Chem.* **1985**, *50*, 1722.

conversion in TLC. Stirring in THF with HF-pyridine also gave no conversion after 2 hours, and the reaction with $BF_3$ etherate only resulted in slow degradation of the compounds to give a complex mixture. In hindsight, the macrolactone **3.122** had probably already been degraded, as indicated by ESI and discussed above, and the subsequent reactions therefore showed unexpected reactivities. Since we had now used all our available advanced intermediates, this disclosed our efforts towards the synthesis of aetheramide B.

In summary, we were able to successfully assemble the core structure of Aetheramide A and B (**3.07** and **3.08**). The peptide coupling of acid **3.117** and amine **3.112** was accomplished under very harsh conditions in 51% yield by forming the acid chloride. The Stille coupling was achieved using Fürstner's "last resort" conditions[294] in a good yield of 63%, but with concomitant cleavage of the TIPS group. For the macrolactonization, we identified DMTMM-$BF_4$ as the best coupling reagent, but still only 15% yield were observed. The formed macrolactone **3.122** also appeared to be rather labile, which ultimately brought our endeavor to a halt.

## 3.6 Conclusions and Outlook

We have successfully assembled the macrocyclic core structure **3.122** of aetheramide B (**3.108**). The dipeptide fragment **3.26** was accessed by enantioselective reduction of an enamide with an excellent e.r. of 98:2. The *syn*-diol fragment **3.27** was prepared from (*R*)-mandelic acid (**3.82**) *via* a Cram chelation-controlled alkynylation, followed by kinetic resolution and hydrostannylation. The key steps in the preparation of the eastern fragment **3.79** were a Grignard addition, CBS reduction and aldol addition to give the advanced intermediate **3.79** in 98:2 e.r. For the coupling of the fragments **3.26** and **3.79**, harsh conditions involving the formation of the acid chloride had to be applied, as milder coupling reagents were not able to couple the sterically very hindered substrates. The subsequent Stille coupling proceeded in good yield applying Fürstner's conditions. Macrolactonization with DMTMM gave the labile macrocycle **3.122** in low yield. Further synthetic transformations towards the target were unsuccessful due to the labile nature of the intermediate **3.122**.

Looking forward, it would be worthwhile to attempt the synthesis by a different fragment assembly sequence, e.g. to form the ester bond first between dipeptide **3.26**

and diol **3.27**, then to perform the peptide coupling reaction and finally establish the core structure *via* a Stille macrocyclization. It should also be noted that the alkyne **3.92** might be transformed to a vinyl boronic acid or ester for Suzuki-Miyaura coupling, giving a more stable intermediate than the stannane **3.27**. The phenolic hydroxy group of the dipeptide fragment **3.26** should not be protected with TIPS, as the group proved to be labile at several stages during the synthesis and eventually was cleaved completely during the Stille reaction. Our robust and well-optimized syntheses of the fragments should be easily modified and would readily give access to the required new compounds.

# 4 Conclusion

In this thesis entitled "*Total Synthesis of (–)-Pyridovericin and Synthetic Studies towards Aetheramide B*" the unique ability of synthetic organic chemistry to achieve desired molecular targets with biological activity was demonstrated.

The second chapter documented the synthesis of the neuritogenic pyridone alkaloid (–)-pyridovericin (**2.46**). The biochemical and biological background of pyridone fungal metabolites were highlighted and previous synthetic efforts summarized. Our synthesis was based on our previously reported syntheses of pyridopolyene natural products. It relied on the coupling of an arylphosphonate to the aldehyde side chain. The enantioselective synthesis of the side chain was achieved by asymmetric hydrogenation in collaboration with the Pfaltz group. (–)-Pyridovericin (**2.46**) was therefore synthesized in 13 linear steps and 22% overall yield. Our modular approach allowed for the generation of structural analogs and we successfully conducted an SAR study in the PC-12 assay to identify highly neuritogenic truncated natural product analogs. We were then able to incorporate the truncated analog in a neuritogenic biocompatible surface material. The work demonstrated the great potential released by synergy of synthetic organic chemistry, biology and material science.

The third chapter described our synthetic efforts towards the HIV-inhibitory depsipeptide Aetheramide B (**3.08**). The development of high yielding and stereospecific routes to three building blocks was reported. The synthesis of the dipeptide fragment **3.26** relied on asymmetric hydrogenation for the introduction of the stereocenter. The synthesis of this fragment was initially accompanied by racemization, but we eventually identified the cause of racemization and developed an alternative route. A chiral pool approach allowed for diastereoselective chelation-controlled alkynylation in the synthesis of the diol fragment **3.27**. The obtained diastereomers were rendered separable by kinetic resolution, and hydrostannylation gave the labile stannane-diol fragment **3.27**. The synthesis of the eastern fragment **3.79** was achieved by a Grignard addition and sequential enantioselective reduction of an enone. The fragments were then successfully coupled to form the macrocylic core **3.122**, but steric hindrance caused all the involving reactions to proceed in low yield. Furthermore, the obtained macrocyle **3.122** proved to be labile and decomposed within hours to a mixture of

unknown byproducts. Nevertheless, with the synthetic knowledge gained and the developed expedient and high yielding routes to the fragments, further pursuit of the target seems to be worthwhile. Our convergent synthetic approach would allow for a streamlined synthesis of structural analogs for SAR studies.

# 5 Experimental Part

## 5.1 List of Abbreviations, Acronyms and Symbols

| | |
|---|---|
| A | activation domain |
| Aβ | amyloid beta protein |
| Ac | acetyl |
| AChE | acetylcholine esterase |
| AcOH | acetic acid |
| AD | Alzheimer disease |
| AIBN | Azobisisobutyronitrile |
| AIDS | acquired immunodeficiency syndrome |
| 6-APA | 6-aminopenicillanic acid |
| 7-ACA | 7-aminocephalosporanic acid |
| ATP | adenosine triphosphate |
| aq. | Aqueous |
| *B. b.* | *Beauveria bassiana* |
| Bn | benzyl |
| brsm | based on recovered starting material |
| °C | degree Celsius |
| c | concentration |
| CAN | cerium (IV) ammonium nitrate |
| Cbz | carboxybenzyl |
| CBS | Corey-Bakshi-Shibata |
| $CH_2Cl_2$ | dichloromethane |
| $CHCl_3$ | chloroform |
| ClpP | Endopeptidase Clp |
| COD | 1,5-cyclooctadiene |
| Cy | cyclisation domain |
| δ | chemical shift |

| | |
|---|---|
| d | doublet |
| D | deuterium |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-en |
| DCC | *N,N'*-Dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DEAD | diethyl azodicarboxylate |
| DIA | *N*,*N*-diisopropyl amine |
| DIBAL-H | diisobutylaluminium hydride |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMEM | Dulbecco's modified Eagle's medium |
| DMF | dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMSO | dimethyl sulfoxide |
| DMTMM | 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium |
| DNA | deoxyribonucleic acid |
| DOS | diversity-oriented synthesis |
| L-DOPA | 3,4-dihydroxyphenylalanine |
| dr | diastereomeric ratio |
| DMS | dimethyl sulfide |
| E | epimerization domain |
| e.e | enantiomeric excess |
| ESI | electrospray ionization |
| Et | ethyl |
| $Et_3N$ | triethylamine |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |

| | |
|---|---|
| EtOH | ethanol |
| eq. | equivalent |
| e.r. | enantiomeric ratio |
| F | formylation domain |
| FTIR | Fourier transform infrared spectroscopy |
| FOS | function-oriented synthesis |
| HAT | histone acetyltransferase |
| HAART | highly active anti retroviral therapy |
| HBTU | *N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate |
| HD | Huntington's disease |
| HDAC | histone deacetylase |
| HIV | human immunodeficiency virus |
| HMPA | Hexamethylphosphoramide |
| HOBt | 1-hydroxybenzotriazol |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| HWE | Horner-Wadswort-Emmons |
| IBX | 2-iodoxybenzoic acid |
| Im | imidazole |
| *J* | coupling constant |
| LDA | lithium diisopropylamide |
| LHMDS | lithium bis(trimethylsilyl)amide |
| m | multiplet |
| *m*-CPBA | meta-chloroperoxybenzoic acid |
| M.p. | melting point |
| Me | methyl |
| MeOH | methanol |
| MEM | minimal essential medium |
| Min | minutes |

| | |
|---|---|
| MOM | methoxymethyl |
| MRSA | Methicillin-resistant Staphylococcus aureus |
| MTPCl | α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride |
| mRNA | messenger ribonucleic acid |
| NBS | N-bromosuccinimide |
| NGF | nerve growth factor |
| NMR | nuclear magnetic resonance spectroscopy |
| NMP | N-methyl-2-pyrrolidon |
| NMT | *N*-methyl transfer domain |
| NOE | nuclear Overhauser effect |
| NRP | non-ribosomal peptide |
| NRPS | non-ribosomoal peptide synthetase |
| PCC | pyridinium chlorochromate |
| PCP | peptide carrier protein |
| PD | Parkinson's disease |
| PDC | pyridinium dichromate |
| Ph | phenyl |
| PKS | polyketide synthase |
| $PPh_3$ | triphenylphosphine |
| PMB | para-methoxybenzyl |
| ppm | parts per million |
| pTsOH | para-toluenesulfonic acid |
| PyBOP | (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate |
| PyBroP | Bromotripyrrolidinophosphonium hexafluorophosphate |
| q | quartet |
| $R_f$ | retention factor |
| RNA | ribonucleic acid |
| (*R,R*)-Et-DUPHOS | (–)-1,2-Bis((2R,5R)-2,5-diethylphospholano)benzene |

| | |
|---|---|
| EDC | 1-(3-dimetylaminopropyl)-3-ethylcarbodiimid |
| r.t. | room temperature |
| s | singlet |
| sat. | saturated |
| SEM | 2-(trimethylsilyl)ethoxymethyl |
| SIV | simian immunodeficiency virus |
| t | triplet |
| T3P | Propylphosphonic anhydride |
| TBAF | tetrabutylammonium fluoride |
| TBS | tert-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TE | thioesterase domain |
| Tf | triflate |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMG | tetramethyl guanidine |
| TPAP | tetrapropylammonium perruthenate |
| $t_R$ | retention time |
| UPLC | ultra high-performance liquid chromatography |
| UV | ultraviolet |
| VMA | vinylogous Mukayama-aldol |
| ν | wavenumber ($cm^{-1}$) |

## 5.2 General Methods and Materials

**Reactions** involving air or moisture sensitive reagents or intermediates were performed under argon in flame-dried glassware. Concentration under reduced pressure or *in vacuo*

was performed by rotary evaporation at 40 °C (unless otherwise specified). Yields refer to purified, dried and spectroscopically pure compounds (>95%) unless stated otherwise.

**Reagents** were purchased from Sigma-Aldrich, Fluorochem, Acros or Alfa and used without further purification unless stated otherwise.

**Solvents** for work-up and chromatography were distilled from technical grade. Solvents used for chemical transformations were either puriss. quality or dried by filtration through activated aluminium oxide under argon or nitrogen ($H_2O$ content <10 ppm, *Karl-Fischer* titration) in a PureSolve MD 5 solvent purification system and stored over 3 Å molecular sieves (20% *v*/*v*).

**Thin layer chromatography** (TLC) was performed on Merck silica gel 60 F254 plates (0.25 mm thickness) precoated with fluorescent indicator. The developed plates were examined under UV light and stained with potassium permanganate followed by heating.

**Flash chromatography** was performed using silica gel 60 (230-240 mesh) from Fluka at 0.3–0.5 bar pressure.

**$^1$H and $^{13}$C NMR spectra** were recorded either using Bruker Avance 400 MHz, Bruker Avance DRX 5500 MHz, or Bruker DRX 600 MHz spectrometers at room temperature. Chemical shifts (δ-values) are reported in ppm and spectra were calibrated related to the solvent residual proton chemical shift and the solvent residual carbon chemical shift.[303] Multiplicity is reported as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved. Coupling constants *J* are reported in Hz.

**Optical rotations** $[\alpha]_D$ were measured at the sodium D line using a 1 mL cell with 1 dm path length on a Jasco P-2000 digital polarimeter at 25 °C. The concentration c is given in g/100 mL in the indicated solvent.

[303] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176.

**Melting points** (M.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected.

**IR spectra** were recorded using a Varian 800 FT-IR ATR Spectrometer. The absorptions are reported in $cm^{-1}$.

**ESI-HRMS** were recorded on a bruker maXis 4G with ESI-UHR-TOF.

**ESI-MS** direct injection measurments were performed on a bruker daltonics esquire 3000 plus mass spectrometer.

**Reversed-phase UPLC-MS** analysis was performed on an Agilent 1290 Infinity LC system with an Eclipse plus C18 (1.8 µm, 50 x 2.1 mm) column and an Agilent Technologies 6130 Quadrupol mass spectrometer using ESI-API. The solvents used were MeCN containing 0.1% trifluoroacetic acid (solvent A) and water containing MeCN 1% and 0.1% trifluoroacetic acid (solvent B). The gradient applied was 0.0-0.4 min 95% B; 0.4 – 3.0 min 95% B -> 95% A; 3.0 – 4.0 min 95% A at a flow rate of 1 mL/min.

**Chiral HPLC** was performed on a Shimadzu UFLC Prominence LC system with a LC-20 AD pump, a DGU-20A3 degasser, a SIL-20A HT Autosampler, a SPD-M20A UV/VIS detector (25 °C) and a CTO-10As oven. The experiments were run with the stated solvent gradients and columns.

**Semi Preparative High Performance Liquid Chromatography** (SP-HPLC) was performed on a Dionex Chromatography System (Interface Chromeleon, ASI 100 automatic sample injector, PDA 100 (USB) PD detector, pump P680). The flow rate was 5 mL/min and a Phenomenex Gemini 5 µm C18 110A column (150 x 10 mm) was used.

**Lyophilisations** were performed with a Christ Freeze Dryer Alpha 1-2 LD plus.
**Microwave reactions** were performed in a Biotage Initiator+ microwave synthesizer in sealable microwave vials.

**Hydrogenation autoclaves** of the type HPM-005 by PREMEX Reactor AG (Lengnau, Switzerland) were used to conduct hydrogenation experiments at the indicated pressures.

## 5.3 Experimental Procedures

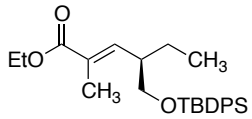
**(*S*)-methyl 2-(((*tert* -butyldiphenylsilyl)oxy)methyl)butanoate (2.70):** A high pressure steel autoclave (Permex Reactor AG; Lengnau, Switzerland; Model HPM-005) with a dry glass insert and a magnetic stir bar was charged with (*E*)-methyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)but-2-enoate (5) (184 mg, 500 μmol, 1.0 eq.) and dry DCM (2.5 mL) before the catalyst [Ir(L)(cod)]$BAr_F$ (1 mol%) was added. The autoclave was closed and attached to a high-pressure hydrogen line and purged with $H_2$. The autoclave was sealed under 50 bar of $H_2$ pressure and the mixture was stirred at 900 rpm for 16 hours at room temperature. After release of $H_2$ the solution was concentrated in a stream of nitrogen, diluted with 1 mL of hexane/MTBE (4:1), and passed through a short plug of silica gel in a Pasteur pipette. The filtrate was concentrated in a stream of nitrogen to give the pure title compound 6 (184 mg, 500 μmol, quant.) with 93:7 *e.r.* All analytical data were in full agreement with previously reported values[304], except for inverted optical rotation of $[\alpha]_D$ = +102 (*c* = 0.89 $CHCl_3$). ***e.r.***: 93:7 determined by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 0.5 mL/min, UV 230 nm) $t_R$ 8.11 (minor), 9.10 (major).

**(*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)butanal (S1):** To a -70 °C cold solution of ester **2.70** (370 mg, 1.04 mmol, 1.0 eq.) in dry DCM (4 mL) was added DIBAL-H (1.15 mL, 1.15 mmol, 1.10 eq., 1.0 M in DCM) portion wise (100 μL every 5 min) in a fashion that the solution was precooled by running down the wall of the flask. This mixture was then stirred at -70 °C for 1 h and then quenched by slow addition of a mixture of MeOH/DCM (1:1 *v/v*, 2 mL) in a fashion that the solution was precooled by running down the wall of the flask. The mixture was diluted with $Et_2O$ (20 mL) and then quickly poured onto a saturated aqueous solution of Seignette's salt (20 mL). The resulting gray slurry was stirred vigorously until two clear layers were observed (~1 h), which then were separated. The aqueous layer was extracted with $Et_2O$ (2 x 20 mL) and the combined organic layers were dried over sodium sulfate, filtered, and the solvents removed *in vacuo*. Flash chromatography ($SiO_2$, pentane/Et2O 15:1) gave the title aldehyde (289 mg, 849 μmol, 82%) as a colorless oil. All analytical data were in full agreement with previously

[304] H. J. Jessen, A. Schumacher, F. Schmid, A. Pfaltz, K. Gademann, *Org. Lett.* **2011**, *13*, 4368.

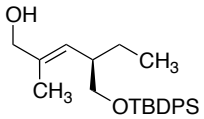
reported values,[304] except for the inverted optical rotation of $[\alpha]_D$ = +16.7 (*c* = 0.83 $CHCl_3$).

**(*R*,*E*)-ethyl-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhex-2-enoate (2.71):**




To a solution of aldehyde **S1** (257 mg, 753 µmol, 1.0 eq.) in dry DCM (3 mL) was added ethyl 2-(triphenylphosphoranylidene)propanoate (409 mg, 1.13 mmol, 1.50 eq.) in one portion. The resulting yellow solution was heated to reflux and the consumption of the aldehyde was followed by $^1$H NMR. After 24 h another portion of the phosphorane (136 mg, 376 µmol, 0.50 eq.) was added and after complete consumption of the aldehyde (48 h) the solvent was removed *in vacuo* and the crude slurry was directly subjected to flash chromatography ($SiO_2$, pentane/$Et_2O$ 25:1) to afford the title compound (304 mg, 715 µmol, 95%, *E*/*Z* >30:1, 91:9 *e.r.*) as a colorless oil. $[\alpha]_D$ = +6.27 (*c* = 0.93 $CHCl_3$). ***e.r.***: 91:9 determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH 99:1, flow rate 0.5 mL/min, UV 206 nm) $t_R$ 11.1 (minor), 11.5 (major). $R_f$ = 0.33 (pentane/$Et_2O$ 15:1). **FTIR** (neat): 2962, 2933, 2859, 1710, 1463, 1388, 1229, 1107, 741, 702 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$): δ = 7.66 – 7.63 (m, 4H,), 7.45 – 7.35 (m, 6H), 6.59 (dq, *J* = 10.3, 1.3 Hz, 1H), 4.28 – 4.14 (m, 2H), 3.63 – 3.53 (m, 2H), 2.60 – 2.50 (m, 1H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.72 – 1.63 (m, 1H), 1.35 – 1.25 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 168.4, 143.9, 135.8, 133.8, 129.8, 129.2, 127.8, 66.4, 60.6, 43.5, 26.9, 24.2, 19.4, 14.5, 13.1, 11.9. **HRMS ESI**: m/z calc. for $C_{26}H_{36}O_3NaSi$ $[M+Na]^+$: 447.2326, found: 447.2319.

**(*R*,*E*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhex-2-en-1-ol (S2):** To a -70 °C cold solution of the ester **2.71** (300 mg, 706 µmol, 1.0 eq.) in dry THF (3 mL) was added drop wise DIBAL-H (2.12 mL, 2.12 mmol, 3.0 eq., 1.0 M in hexane). The solution was then stirred 20 min at -70 °C, then 30 min at 0 °C and finally 1 h at r.t., after which TLC indicated complete consumption of the starting material. The reaction was quenched by *drop wise* addition of MeOH (2 mL), diluted with $Et_2O$ (20 mL) and then quickly poured onto a saturated aqueous solution of Seignette's salt (20 mL). The resulting gray slurry was stirred vigorously until two clear layers were observed (ca. 2 h), which then were separated.



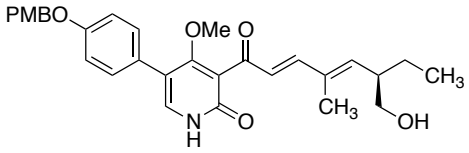
The aqueous layer was extracted with $Et_2O$ (2 x 20 mL) and the combined organic layers were dried over sodium sulfate, filtered, and the solvents removed *in vacuo*. Flash chromatography ($SiO_2$, pentane/$Et_2O$ 4:1) gave the title compound (249 mg, 621 µmol, 88%, *E*/*Z* >30:1, 89:11 *e.r.*) as a colorless oil. $[\alpha]_D$ = -24.6 (*c* = 1.1 $CHCl_3$). ***e.r.***: 89:11 determined by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 99:1, flow rate 0.6 mL/min, UV 206 nm) $t_R$ 15.3 (major), 17.3 (minor). $R_f$ = 0.30 (pentane/Et2O 4:1). **FTIR** (neat): 3324 (br), 2958, 2930, 2857, 1389, 1427, 1111, 1007, 702 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 7.69 – 7.64 (m, 4H), 7.45 – 7.35 (m, 6H), 5.13 (dq, *J* = 9.8, 1.1 Hz, 1H), 3.98 (d, *J* = 5.9 Hz, 2H), 3.60 – 3.50 (m, 2H), 2.48 – 2.37 (m, 1H), 1.71 – 1.58 (m, 1H), 1.62 (d, *J* = 1.1 Hz, 3H), 1.27 – 1.15 (m, 2H), 1.05 (s, 9H), 0.84 (t, *J* = 7.4 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 136.4, 135.8, 134.2, 129.7, 128.0, 127.7, 69.1, 67.2, 42.3, 27.0, 24.7, 19.4, 14.3, 11.8. **HRMS ESI**: m/z calc. for $C_{24}H_{35}O_2Si$ $[M+H]^+$: 383.2401, found: 383.2401.

**(*R*,*E*)-4-(hydroxymethyl)-2-methylhex-2-enal (S3):** To a solution of alcohol **S2** (160 mg, 397 µmol, 1.0 eq.) in dry DCM (3 mL) was added powdered molecular sieves (50 mg, 4 Å, oven-dried at 120 °C) and *N*-methylmorpholine *N*-oxide (70.0 mg, 596 µmol, 1.50 eq.). To this slurry, tetrapropylammonium perruthenate (3.50 mg, 10.0 µmol, 2.5 mol%) was added and the resulting black suspension was stirred for 1 h at r.t. after which TLC indicated complete consumption of the starting material. The crude mixture was filtered over a plug of silica, which was further washed with DCM (70 mL). The solvents were removed *in vacuo* to give the protected aldehyde **S4** as a yellow oil (155 mg, 397 µmol, 99%), which was used without further purification in the next step. $R_f$ = 0.45 (pentane/$Et_2O$ 10:1) **$^1$H NMR** (500 MHz, $CDCl_3$) δ = 9.37 (s, 1H), 7.64 – 7.60 (m, 4H), 7.46 – 7.35 (m, 6H), 6.27 (dq, *J* = 10.2, 1.3 Hz, 1H), 3.70 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.62 (dd, *J* = 10.0, 6.6 Hz, 1H), 2.73 (dddt, *J* = 10.2, 9.0, 6.4, 5.2 Hz, 1H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.71 – 1.62 (m, 1H), 1.41 – 1.31 (m, 1H), 1.03 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 195.5, 156.7, 135.6, 135.5, 129.8, 127.7, 66.1, 43.7, 26.8, 24.0, 11.7, 9.7.

To a solution of the crude aldehyde **S4** (179 mg, 447 µmol, 1.0 eq.) in dry THF (3 mL) was added TBAF (450 µL, 450 µmol, 1.0 eq., 1.0 M in THF) and the resulting dark yellow solution was stirred at r.t. After 2 h, UPLC-MS indicated complete consumption of the starting material and the reaction was poured on saturated aqueous $NH_4Cl$ (10

mL) and extracted with $Et_2O$ (5 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and the solvents removed *in vacuo*. Flash chromatography ($SiO_2$, pentane/$Et_2O$ 1:10) gave the deprotected aldehyde **S3** (60.3 mg, 424 µmol, 95%, E/Z >30:1) as a colorless oil. $[\alpha]_D$ = -26.6 (*c* = 0.90 $CHCl_3$). $R_f$ = 0.45 (pentane/$Et_2O$ 1:10). **FTIR** (neat): 3363 (br), 2962, 2931, 2876, 2361, 2335, 1685, 1042, 766 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 9.45 (s, 1H), 6.32 (dq, *J* = 10.1, 1.3 Hz, 1H), 3.75 – 3.60 (m, 2H), 2.84 – 2.71 (m, 1H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.72 – 1.62 (m, 1H), 1.46 – 1.34 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$): δ = 195.3, 155.5, 141.4, 65.6, 43.9, 24.1, 11.8, 10.0. **HRMS ESI**: m/z calc. for $C_8H_{15}O_2$ $[M+H]^+$: 143.1067, found: 143.1066.

**3-((*R*,2*E*,4*E*)-6-(hydroxymethyl)-4-methylocta-2,4-dienoyl)-4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)pyridin-2(1H)-one (S5):** To a suspension of the aldehyde **S3** (36.0 mg, 253 µmol, 1.20 eq.) and the phosphonate **2.57** (103 mg, 211 µmol, 1.0 eq.) in THF/$H_2O$ (1 mL, 4:1 *v*/*v*) was added LiOH•$H_2O$ (17.7 mg, 422 µmol, 2.0 eq.). A yellow solution formed immediately, which was stirred under exclusion of light at r.t. and monitored by UPLC-MS. After 6 days, the dark orange reaction mixture was poured on saturated aqueous $NH_4Cl$ (10 mL) and extracted with EtOAc (4 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and the solvents removed *in vacuo*. Flash chromatography ($SiO_2$, DCM/MeOH 20:1) gave the pyridopolyene **S5** (82.0 mg, 162 µmol, 77%, *E*/*Z* >30:1) as a yellow oil. $R_f$ = 0.30 (DCM/MeOH 20:1). **FTIR** (neat): 3400 (br), 2934, 2358, 1634, 1611, 1512, 1237, 1033, 830, 733 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$): δ = 12.91 (s (br), 1H), 7.40 – 7.35 (m, 3H), 7.32 – 7.27 (m, 2H), 7.22 (d, *J* = 15.8 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.95 – 6.91 (m, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.74 (d, *J* = 10.1 Hz, 1H), 5.01 (s, 2H), 3.82 (s, 3H), 3.64 – 3.59 (m, 1H), 3.61 (s, 3H), 3.52 – 3.46 (m, 1H), 2.68 – 2.58 (m, 1H), 1.89 (d, *J* = 1.0 Hz, 3H), 1.59 – 1.52 (m, 1H), 1.32 – 1.22 (m, 1H), 0.86 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 194.2, 168.4, 165.6, 164.4, 159.7, 158.7, 150.6, 145.4, 145.2, 136.0, 135.2, 130.0, 129.4, 129.3, 126.9, 126.4, 114.8, 113.9, 69.8, 68.8, 60.7, 55.2, 43.9, 24.2, 13.0, 11.6. **HRMS ESI**: m/z calc. for $C_{30}H_{34}O_6N$ $[M+H]^+$: 504.2381, found: 504.2377.

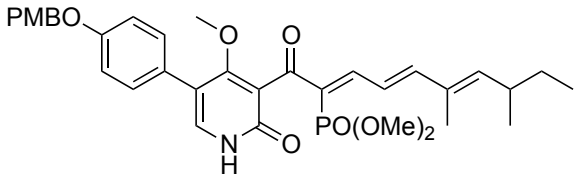


**(–)-Pyridovericin (2.46):** A suspension of the pyridopolyene **S5** (74.0 mg, 147 µmol, 1.0 eq.), LiI•3$H_2O$ (111 mg, 589 µmol mol, 4.0 eq.) and pyridine hydrochloride (102 mg, 883 µmol, 6.0 eq.) in degassed (freeze/thaw) THF (4 mL) was heated to 60 °C for 4 h in a microwave reactor. The yellow suspension was poured on brine (5 mL) and then extracted with DCM (3 x 7 mL). The combined organic layers were dried over sodium sulfate, filtered, and the solvents removed *in vacuo*. Flash chromatography ($SiO_2$, DCM/MeOH 20:1) gave the crude demethylated pyridone **S6** (51.0 mg, 104 µmol, 71%, *E*/*Z* > 5:1) as a yellow oil. $^1$H NMR data is given for the *E* isomer. $\boldsymbol{R_f}$ = 0.40 (DCM/MeOH 15:1). **$^1$H NMR** (400 MHz, $CDCl_3$): δ = 11.59 (s, 1H), 7.98 (d, *J* = 15.4 Hz, 1H), 7.62 (d, *J* = 15.4 Hz, 1H), 7.44 – 7.33 (m, 5H), 7.07 – 6.98 (m, 2H), 6.98 – 6.89 (m, 2H), 5.82 (d, *J* = 10.0 Hz, 1H), 5.01 (s, 2H), 3.82 (s, 3H), 3.71 – 3.60 (m, 1H), 3.56 – 3.45 (m, 1H), 2.75 – 2.60 (m, 1H), 1.94 (s, 3H), 1.63 – 1.53 (m, 1H), 1.34 – 1.24 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H).

The crude pyridone **S6** (16.0 mg, 33.0 µmol, 1.0 eq.) was suspended in DCM (2 mL) and trifluoroacetic acid (100 µL, 5% *v*/*v* in DCM) was added drop wise. The formed yellow solution was stirred at r.t. for 30 min, after which TLC indicated complete consumption of the starting material. The crude solution was poured on saturated aqueous $NaHCO_3$ (5 mL) and extracted with a mixture of DCM/MeOH/EtOAc (6:1:1 v/v, 5 x 10 mL), after which the aqueous layer was colorless. The combined yellow organic layers were dried over sodium sulfate, filtered, and the solvents removed *in vacuo*. Flash chromatography ($SiO_2$, DCM/MeOH 20:1) gave (-)-Pyridovericin (**2.46**) (10 mg, 27 µmol, 83%, *E*/*Z*>6:1) as a yellow oil. Fractional crystallization was achieved by dissolving the crude material in MeOH/DCM (1:9 v/v, 300 µL) and drop wise addition of pentane (1.20 mL) while swirling vigorously. The yellow suspension was stored at 5 °C for 10 min, centrifuged and the supernatant removed carefully with a syringe. After 5 repetitions of the process, this gave an analytical sample (3 mg) of 1 as an amorphous yellow solid with *e.r.* 93:7 and an *E*/*Z* ratio >30:1. $\boldsymbol{[\alpha]_D}$ = -10.8 (*c* = 0.16 MeOH). ***e.r.***: 93:7 determined by HPLC (Chiralcel IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV 206 nm) $t_R$ 8.3 (minor), 9.2 (major). $\boldsymbol{R_f}$ = 0.17 (DCM/MeOH 15:1). **FTIR** (neat): 3287 (br), 2960, 2929, 2360, 2341, 1648, 1610, 1518, 1460, 1263, 1215, 1037, 985, 835, 769 cm$^{-1}$. **$^1$H NMR** (600 MHz, DMSO): δ = 17.56 (s, 1H), 11.62

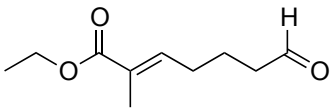
(s, 1H), 9.48 (s, 1H), 7.99 (d, *J* = 14.9 Hz, 1H), 7.55 (s, 1H), 7.51 (d, *J* = 15.6 Hz, 1H), 7.30 – 7.24 (m, 2H), 6.81 – 6.75 (m, 2H), 5.94 (d, *J* = 9.6 Hz, 1H), 4.59 (t, *J* = 5.4 Hz, 1H), 3.41 – 3.30 (m, 2H), 2.57 – 2.49 (m, 1H), 1.85 (s, 3H), 1.65 – 1.54 (m, 1H), 1.28 – 1.17 (m, 1H), 0.82 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR** (151 MHz, DMSO): δ = 193.7, 176.9, 161.8, 156.7, 149.4, 147.5, 140.7, 134.5, 130.1, 123.5, 123.1, 115.0, 112.8, 106.0, 64.0, 43.6, 24.0, 12.8, 11.7. **HRMS ESI**: m/z calc. for $C_{21}H_{24}O_5N$ $[M+H]^+$: 370.1649, found: 370.1647. **$\lambda_{max}$** (MeCN/H2O 60:40): 206, 249, 338 nm.

**Dimethyl ((2*Z*,4*E*,6*E*)-1-(4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)-6,8-dimethyl-1-oxodeca-2,4,6-trien-2-yl)phosphonate (2.74):**



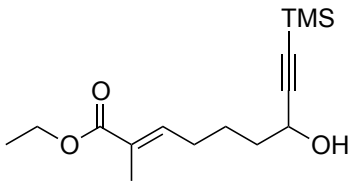

The phosphonate **2.57** (9.50 mg, 20.0 µmol, 1.0 eq.) and aldehyde **2.72** (5.70 mg, 19.5 µmol, 1.0 eq.) were suspended in dry THF (300 mL) and one drop of DBU was added. The suspension was stirred for 24 h at r.t. under exclusion of light, poured on saturated aqueous $NH_4Cl$ (2 mL), extracted with DCM (5 x 3 mL), dried over sodium sulfate and evaporated. The crude yellow oil was purified by flash chromatography ($SiO_2$, DCM/MeOH 20:1) to give the HWE product (4.0 mg, 7.8 µmol, 40%) and the crude Knoevenagel product. This was further purified by semi preparative HPLC (5 – 100% MeCN in $H_2O$ in 25 min) to give the Knoevenagel product **2.74** (4.0 mg, 6.4 µmol, 30%) as a mixture of 4 *E*/*Z* isomers. NMR data is given for the major all-*E* isomer. Most proton shifts were assigned from 2D-NMR spectra. The signal of the carbon atom at the C(3) position of the pyridone could not be detected. ***R*$_f$** = 0.15 (DCM/MeOH 20:1). **FTIR** (neat): 2957, 2853, 2361, 1589, 1643, 1513, 1462, 1387, 1292, 1243, 1177, 1030, 791, 649 $cm^{-1}$. **$^1$H NMR** (600 MHz, $CDCl_3$): δ = 12.62 (s (br), 1H), 7.62 (dd, *J* = 14.7, 11.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.27 (s, 1H), 7.27 (dd, *J* = 33.0, 11.6 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 14.7 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 2H), 5.67 (d, *J* = 9.7 Hz, 1H), 5.01 (s, 2H), 3.83 (d. *J* = 2.8 Hz, 6H), 3.74 (s, 3H), 3.58 (s, 3H), 2.50 – 2.39 (m, 1H), 1.87 (s, 3H), 1.44 – 1.35 (m, 1H), 1.33 – 1.22 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.82 (t, *J* = 7.40 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$): δ = 193.0, 168.2, 165.0, 163.6, 162.2, 160.7, 159.5, 158.5, 154.8, 149.7, 134.9, 133.7, 130.0, 129.2, 128.9, 123.2, 117.0, 114.9, 114.0, 69.8, 60.4, 54.3, 52.8, 35.0, 29.8, 20.1, 12.7, 11.9. **$^{31}$P NMR** (243 MHz, $CDCl_3$): δ = 17.1. **HRMS ESI**: m/z calc. for $C_{34}H_{41}O_8NP$ $[M+H]^+$: 622.2564, found: 622.2565.

**(*E*)-ethyl 2-methyl-7-oxohept-2-enoate (3.31):**[305] A commercial solution of glutaric aldehyde **3.30** (20 mL, 50% *v*/*v* in water) was diluted with $Et_2O$ (100 mL), extracted with brine (3 x 30 mL) and dried over sodium sulfate, which gave after filtration and evaporation of solvent spectroscopically ($^1$H NMR) pure glutaric aldehyde.



To a solution of glutaric aldehyde **3.30** (6.60 g, 65.9 mmol, 5.0 eq.) in Dichloromethane (15 mL) was added (Carbethoxyethylidene)triphenylphosphorane (4.78 g, 13.2 mmol, 1.0 eq.) and the resulting yellow solution heated to reflux for 18 h. Removal of the solvent gave a yellow oil which was directly purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 7:2) to give the pure *E*-isomer of the ester **3.31** as a yellow oil (1.53 g, 8.30 mmol, 63%). All analytical data were in full agreement with the literature. $\boldsymbol{R_f}$ = 0.28 ($SiO_2$, pentane/$Et_2O$, 7:2). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.78 (t, *J* = 1.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 1.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 3H), 2.47 (td, *J* = 7.3, 1.5 Hz, 2H), 2.22 (q, *J* = 7.4 Hz, 3H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.81 – 1.77 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 201.97, 168.15, 140.55, 129.08, 60.66, 43.34, 27.92, 21.12, 14.41, 12.55. sf266

**(*E*)-ethyl 7-hydroxy-2-methyl-9-(trimethylsilyl)non-2-en-8-ynoate (S7):** To a -70 °C cold solution of Trimethylsilyl acetylene (960 mg, 9.77 mmol, 1.20 eq.) in THF (15 mL) was added drop wise a solution of *n*-BuLi (5.40 mL, 8.60 mmol, 1.10 eq., 1.6 M in hexane) and then stirred for 10 min. The solution was then warmed to 0 °C for 10 min before being cooled to -70 °C and cannulated to a -70 °C cold solution of the aldehyde **3.31** (1.53 g, 8.14 mmol, 1.0 eq.) in THF (16 mL). The mixture was stirred for 10 min, after which the cooling bath was removed and the yellow solution was stirred at r.t. for 4 h, after which $^1$H NMR indicated complete consumption of the aldehyde. The reaction was quenched by slow addition of saturated aqueous $NH_4Cl$ (20 mL), and the aqueous layer was extracted with $Et_2O$ (3 x 20 mL). The unified organic layers were dried over sodium sulfate, filtered, the solvents removed and the obtained crude yellow oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 4:1) to give the pure *E*-isomer of the alcohol **S7** as a colorless oil (2.22 g,

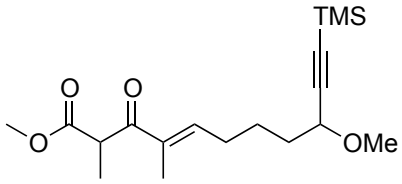


[305] E. L. Richards, P. J. Murphy, F. Dinon, S. Fratucello, P. M. Brown, T. Gelbrich, Michael B. Hursthouse, *Tetrahedron* **2001**, *57*, 7771.

7.39 mmol, 91%). $R_f$ = 0.41 ($SiO_2$, pentane/$Et_2O$, 4:1). **FTIR** (neat): 3419 (br), 2957, 1709, 1249, 1093, 841, 630 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.73 (td, *J* = 7.4, 1.3 Hz, 1H), 4.35 (t, *J* = 6.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.27 – 2.12 (m, 3H), 1.81 (d, *J* = 0.7 Hz, 3H), 1.76 – 1.67 (m, 2H), 1.66 – 1.57 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.15 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.34, 141.71, 128.31, 106.70, 89.62, 62.60, 60.57, 37.26, 28.31, 24.27, 14.37, 12.48, -0.04. **HRMS ESI** calc. for $C_{15}H_{27}O_3Si^+$ $[M+H]^+$: 283.1724, found 283.1723. sf268

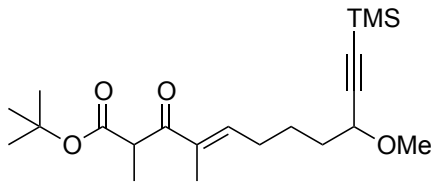
**(*E*)-ethyl 7-methoxy-2-methyl-9-(trimethylsilyl)non-2-en-8-ynoate (3.32):** To a -70 °C cold solution of the alcohol **S7** (190 mg, 654 mmol, 1.0 eq.) in THF (3.0 mL) was added drop wise a solution of *n*-BuLi (500 mL, 780 mmol, 1.10 eq., 1.6 M in Hexane). The resulting yellow solution was stirred for 20 min, after which methyl iodide (370 mL, 5.90 mmol, 9.0 eq.) was added drop wise. After 20 min of stirring, the temperature was raised to -30 °C and DMSO (190 mL, 2.60 mmol, 4.0 eq.) was added in one portion upon which a colorless precipitate formed. The stirred suspension was allowed to warm to r.t. overnight, after which TLC indicated complete consumption of the alcohol. The reaction was quenched by slow addition of saturated aqueous $NH_4Cl$ (10 mL), and the aqueous layer was extracted with $Et_2O$ (5 x 15 mL). The unified organic layers were dried over sodium sulfate, the solvents removed and the obtained crude oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 15:1) to give the alcohol **3.32** as a colorless oil (153 mg, 516 mmol, 79%, *E*/*Z* > 9:1). $R_f$ = 0.25 ($SiO_2$, pentane/$Et_2O$, 15:1). **FTIR** (neat): 2955, 2171, 1709, 1250, 1106, 841, 760, 666 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.74 (t, *J* = 7.4 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.92 (t, *J* = 6.3 Hz, 1H), 3.38 (s, 3H), 2.20 (q, *J* = 7.3 Hz, 2H), 1.82 (s, 3H), 1.77 – 1.66 (m, 2H), 1.64 – 1.51 (m, 2H), 1.31 – 1.26 (t, *J* = 7.3 Hz, 3H), 0.17 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.34, 141.76, 128.30, 104.34, 90.94, 71.46, 60.54, 56.50, 35.20, 28.42, 24.39, 14.42, 12.51, 0.06. **HRMS ESI** calc. for $C_{16}H_{29}O_3Si^+$ $[M+H]^+$: 297.1880, found 297.1880. sf212

**(*E*)-methyl 9-methoxy-2,4-dimethyl-3-oxo-11-(trimethylsilyl)undec-4-en-10-ynoate (S8):** To a 0 °C cold solution of diisopropyl amine (81.0 mg, 801 mmol, 2.50 eq.) in




THF (1.0 mL) was added drop wise a solution of *n*-BuLi (500 mL, 800 mmol, 2.50 eq., 1.6 M in hexane) and the resulting solution was stirred for 20 min before being cooled to -70 °C. A Solution of methyl propionate (70.6 mg, 801 mmol, 2.5 eq.) in THF (1.0 mL) was added drop wise and after 1 h of stirring, a solution of the ester **S7** (100 mg, 320 mmol, 1.0 eq.) in THF (1.0 mL) was added drop wise. TLC indicated complete consumption of the starting material after 2 h of stirring. The reaction was quenched by slow addition of saturated aqueous $NH_4Cl$ (10 mL), and the aqueous layer was extracted with $Et_2O$ (5x10 mL). The unified organic layers were dried over sodium sulfate, the solvents removed and the obtained crude oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 4:1) to give the b-keto ester **S8** as a colorless oil (63.0 mg, 182 mmol, 57%, *E*/*Z* >30:1). $\boldsymbol{R_f}$ = 0.35 ($SiO_2$, pentane/$Et_2O$, 4:1). **FTIR** (neat): 2953, 1741, 1669, 1453, 1249, 1107, 842, 760, 666 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.66 (td, *J* = 7.2, 1.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 1H), 3.68 (s, 3H), 3.39 (s, 3H), 2.29 (dt, *J* = 13.2, 6.8 Hz, 2H), 1.80 (s, 3H), 1.76 – 1.69 (m, 2H), 1.67 – 1.59 (m, 2H), 1.36 (d, *J* = 7.1 Hz, 3H), 0.18 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 197.35, 171.91, 143.83, 136.85, 104.17, 91.11, 71.36, 71.34, 56.57, 52.49, 46.74, 35.17, 28.98, 24.34, 24.33, 14.34, 11.81, 0.06. **HRMS ESI** calc. for $C_{18}H_{30}NaO_4Si^+$ $[M+Na]^+$:: 361.1806, found 361.1806. sf296

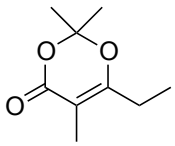
**(*E*)-*tert*-butyl 9-methoxy-2,4-dimethyl-3-oxo-11-(trimethylsilyl)undec-4-en-10-**




**ynoate (S9):** To a 0 °C cold solution of diisopropyl amine (46.0 mg, 450 mmol, 3.0 eq.) in THF (0.5 mL) was added drop wise a solution of *n*-BuLi (280 mL, 450 mmol, 3.0 eq., 1.6 M in hexane) and the resulting solution was stirred for 20 min before being cooled to -70 °C. A Solution of *tert*-butyl propionate (59.0 mg, 450 mmol, 3.0 eq.) in THF (0.5 mL) was added drop wise and after 1 h of stirring, a solution of the ester **S7** (47 mg, 0.15 mmol, 1.0 eq.) in THF (0.5 mL) was added drop wise. The reaction was allowed to warm to r.t. overnight, and the reaction was quenched by slow addition of saturated aqueous $NH_4Cl$ (5 mL) and the aqueous layer was extracted with $Et_2O$ (5 x 5 mL). The unified organic layers were dried over sodium sulfate, the solvents removed and the obtained crude oil was purified

by flash chromatography ($SiO_2$, pentane/$Et_2O$ 10:1) to give the β-keto ester **S9** as a colorless oil (39.1 mg, 100 mmol, 68%, *E*/*Z* >15:1). $\boldsymbol{R_f}$ = 0.15 ($SiO_2$, pentane/$Et_2O$ 10:1). **FTIR** (neat): 2938, 2363, 1731, 1672, 1368, 1249, 1151, 1108, 842, 760 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.64 (td, *J* = 7.2, 1.2 Hz, 1H), 4.0 (q, *J* = 7.0 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 1H), 3.39 (s, 3H), 2.29 (q, *J* = 7.2 Hz, 2H), 1.80 (d, *J* = 0.8 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.68 – 1.58 (m, 2H), 1.41 (s, 9H), 1.31 (d, J = 7.0 Hz, 3H), 0.18 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 197.69, 170.74, 142.87, 137.05, 104.20, 91.07, 81.40, 71.38, 56.56, 48.16, 35.25, 28.97, 28.02, 24.43, 14.04, 11.91, 0.08. **HRMS ESI** calc. for $C_{21}H_{37}O_4Si^+$ $[M+H]^+$: 381.2456, found 381.2450. sf272

**6-Ethyl-2,2,5-trimethyl-4*H*-1,3-dioxin-4-one (3.40):**[306] To a 500 mL round bottom flask charged with flame dried potassium carbonate (114 g, 882 mmol, 4.0 eq.) and THF (250 mL) was added methyl 3-oxovalerate (26.5 mL, 206 mmol, 1.0 eq.). The mixture was stirred vigorously for 10 min after which methyl iodide (14.1 mL, 226 mmol, 1.10 eq.) was added slowly and the mixture was heated to reflux for 15 h, after which $^1$H NMR indicated complete consumption of the starting material (additional methyl iodide was added and refluxing was continued in case of incomplete transformation). The mixture was allowed to warm to r.t., filtered over a plug of diatomaceous earth and washed with $Et_2O$ (150 mL) to give after removal of solvent methyl 2-methyl-3-oxopentanoate (22.1 g, 206 mmol, quant.), which was used in the next step without further purification. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 3.72 (s, 3H), 3.53 (q, *J* = 7.2 Hz, 1H), 2.69 – 2.42 (m, 2H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H). sf318



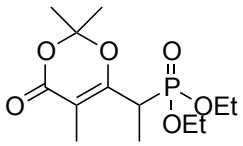
To a 0 °C cold solution of methyl 2-methyl-3-oxopentanoate (2.50 g, 16.5 mmol, 1.0 eq.) in MeOH/$H_2O$ (16.5 mL, 1:1 *v*/*v*) was added KOH (1.09 g, 16.5 mmol, 1.0 eq.) in one portion. After stirring for 1 h at r.t. TLC indicated complete consumption of the starting material, the reaction was adjusted to pH 7–8 with saturated aqueous $NH_4Cl$ (20 mL) and then to pH 1 by *careful* addition of aqueous HCl (1 M) – excess HCl causes decarboxylation! The aqueous layer was extracted with $Et_2O$ (5 x 20 mL), dried over sodium sulfate and filtered. The solvent was removed carefully on the rotavap (20 °C water bath temperature) to give the product 2-methyl-3-oxopentanoic acid (2.19 g, 16.8

[306] H. Shimamura, T. Sunazuka, T. Izuhara, T. Hirose, K. Shiomi, S. Ōmura, *Org. Lett.* **2007**, *9*, 65; A. Kamal, A. A. Shaik, S. Azeeza, M. S. Malik, M. Sandbhor, *Tetrahedron: Asymmetry* **2006**, *17*, 2890.

mmol, quant.) as a colorless oil, which was used without further purification in the next step. Care must be taken to remove all methanol and water from the crude material, as the subsequent dioxinone formation reaction is sensitive to residual solvent. However, prolonged drying on the rotavap under vacuum causes decarboxylation. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 12.52 (s, 1H), 3.56 (q, *J* = 7.2 Hz, 1H), 2.74 – 2.51 (m, 2H), 1.37 (dd, *J* = 6.4, 0.8 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H). sf319

To a 0 °C cold solution of 2-methyl-3-oxopentanoic acid (15.0 g, 116 mmol, 1.0 eq.) in dry acetone (39 mL) was added acetic anhydride (21.6 mL, 231 mmol, 2.0 eq., freshly filtered over basic aluminum oxide) and sulfuric acid (1.54 mL, 28.8 mmol, 0.25 eq.) after 30 min, the yellow solution was allowed to warm to r.t. and stirred overnight, after which TLC indicated complete consumption of the starting material. The formed dark red suspension was poured carefully on saturated aqueous bicarbonate (200 mL) and extracted with $Et_2O$ (200 mL). The organic layer was extracted with saturated aqueous bicarbonate (200 mL), and the combined aqueous layers were extracted with $Et_2O$ (2 x 200 mL). Drying over sodium sulfate and filtration gave a crude yellow oil, which was distilled to afford the title compound **3.40** (12.7 g, 74.8 mmol, 65%) as a colorless oil. Distillation can be reapplied if required. All analytical data were in full agreement with the reported literature values. **B.p.** 54 °C (0.01 mbar). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 2.29 (q, *J* = 7.6 Hz, 2H), 1.82 (s, 3H), 1.64 (s, 6H), 1.11 (t, *J* = 7.6 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 166.91, 163.13, 104.77, 99.64, 25.19, 24.42, 10.43, 9.99. sf323

**Diethyl (1-(2,2,5-trimethyl-4-oxo-4H-1,3-dioxin-6-yl)ethyl)phosphonate (3.44):** The

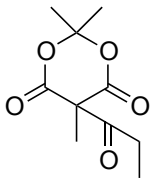



compound was prepared in analogy to a literature procedure.[307] To a -70 °C cold solution of LDA (840 mL, 1.67 mmol, 1.50 eq., 2.0 M in THF) was cannulated a -70 °C solution of dioxinone **3.40** (200 mg, 1.12 mmol, 1.0 eq.) in THF (1.1 mL) and the resulting orange mixture was stirred for 20 min at -25 °C before being cooled to -70 °C. Diethyl chlorophosphite (340 mL, 2.20 mmol, 2.0 eq.) was added drop wise and after 20 min of stirring, the yellow solution was stirred at r.t. for 20 min, upon which a suspension had formed. DCM (3.5 mL) and hydrogen peroxide (4.0 mL, 30% aqueous solution) were added subsequently and the biphasic mixture was stirred vigorously for 30 min. The mixture was poured on

[307] R. K. Boeckman Jr., T. M. Kamenecka, S. G. Nelson, J. R. Pruftt, Thomas E. Barta, *Tetrahedron Letters* **1991**, *23*, 2581.

brine (10 mL) and the aqueous layer was extracted with DCM (3 x 10 mL). Drying over sodium sulfate, filtration and removal of solvent gave a crude yellow oil, which was purified by flash chromatography ($SiO_2$, EtOAc) to give the phosphonate **3.44** as a colorless oil (107 mg, 349 mmol, 31%). $\boldsymbol{R_f}$ = 0.35 ($SiO_2$, EtOAc). **FTIR** (neat): 3479 (br), 2985, 2927, 1721, 1640, 1357, 1240, 1155, 1019, 920, 666 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 4.22 – 4.07 (m, 4H), 3.19 (dq, *J* = 22.9, 7.2 Hz, 1H), 1.86 (d, *J* = 3.4 Hz, 3H), 1.66 (d, *J* = 5.5 Hz, 6H), 1.40 (dd, *J* = 18.2, 7.2 Hz, 3H), 1.32 (td, *J* = 7.1, 0.5 Hz, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 162.55 (d, *J* = 2.3 Hz), 161.01 (d, *J* = 10.6 Hz), 105.25 (s), 102.55 (d, *J* = 9.5 Hz), 62.55 (d, *J* = 7.1 Hz), 62.44 (d, *J* = 6.9 Hz), 35.42 (s), 34.04 (s), 25.68 (s), 24.23 (s), 16.48 (d, *J* = 5.9 Hz), 11.16 (d, *J* = 5.8 Hz), 10.35 (d, *J* = 1.5 Hz). **HRMS ESI** calc. for $C_{13}H_{24}OP^+$ $[M+H]^+$: 307.1305, found 307.1306. sf332

**2,2,5-Trimethyl-5-propionyl-1,3-dioxane-4,6-dione (S10):** The compound was



prepared in analogy to a literature procedure.[308] To a -70 °C cold solution of methyl Meldrum's acid (330 mg, 2.09 mmol, 1.0 eq.) in DCM (4.0 mL) was added pyridine (340 mL, 4.20 mmol, 2.0 eq.) and drop wise propionyl chloride (220 mL, 2.20 mmol, 2.0 eq.). After 10 min, the solution was warmed to r.t. and stirred for 2 h, upon which $^1$H NMR indicated complete consumption of the starting material. The orange suspension was diluted with DCM (5 mL), poured on aqueous HCl (10 mL, 2 M) and the aqueous layer was extracted with DCM (2 x 10 mL). The unified organic layers were dried over sodium sulfate, filtered and the solvents removed *in vacuo*. The obtained crude yellow oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 1:1) to give the title compound **S10** as a colorless crystalline solid (346 mg, 1.62 mmol, 77%). $\boldsymbol{R_f}$ = 0.45 ($SiO_2$, pentane/$Et_2O$ 1:1). **FTIR** (neat): 2948, 1748, 1736, 1717, 1380, 1298, 1204, 1101, 1071, 972, 883 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 2.71 (q, *J* = 7.1 Hz, 1H), 1.87 (s, 1H), 1.75 (d, *J* = 4.9 Hz, 2H), 1.18 (t, *J* = 7.4 Hz, 1H), 1.10 (t, *J* = 7.1 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 199.58, 165.23, 106.30, 100.14, 31.84, 29.44, 28.38, 20.61, 8.0. **HRMS ESI** calc. for $C_{10}H1_4NaO_5^+$ $[M+Na]^+$: 237.0733, found 237.0732. sf303

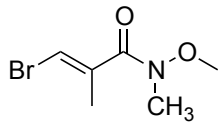
[308] E. Bourcet, F. Fache, O. Piva, *Tetrahedron* **2010**, *66*, 1319.

***N*-methoxy-*N*-methylmethacrylamide (S11):** The compound was prepared according to a literature procedure.[309] To a -20 °C cold solution of *N,O*-dimethylhydroxylamine hydrochloride (1.94 g, 20.0 mmol, 1.0 eq.) in dry DCM (40 mL) was slowly added pyridine (4.0 mL, 50.0 mmol, 2.50 eq.) and the mixture was stirred for 20 min. Methacryloyl chloride (2.10 mL, 20.0 mmol, 1.0 eq.) was then added drop wise to the suspension and the reaction was allowed to warm to r.t.. After 2 h of stirring, $^{1}$H NMR indicated complete consumption of the starting material. The solvent was removed and the residue dissolved in $Et_2O$/DCM (30 mL, 1:1 *v/v*), washed with HCl (2 x 20 mL, 1 M) and saturated aqueous sodium carbonate solution (2 x 20 mL) and the organic layer was dried over sodium sulfate and filtered. Removal of solvents and drying under high vacuum gave the Weinreb amide **S11** as a colorless oil (2.38 g, 18.4 mmol, 93%), which was used without further purification. All analytical data were in full agreement with the reported literature values. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 5.30 (dd, *J* = 3.1, 2.0 Hz, 1H), 5.25 – 5.21 (m, 1H), 3.65 (s, 3H), 3.23 (s, 3H), 1.98 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 171.69, 140.34, 117.50, 61.35, 33.45, 20.04. sf347

**2-Methyl-1-morpholinoprop-2-en-1-one (S12):** To a -20 °C cold solution of morpholine (6.10 mL, 70.0 mmol, 3.50 eq.) in dry DCM (40 mL) was slowly added methacryloyl chloride (2.10 mL, 20.0 mmol, 1.0 eq.) and the reaction was allowed to warm to r.t. After 1 h of stirring, $^{1}$H NMR indicated complete consumption of the starting material. The solvent was removed and the residue dissolved in $Et_2O$/DCM (30 mL, 1:1 *v/v*), washed with aqueous HCl (2 x 20 mL, 1 M) and saturated aqueous sodium carbonate solution (2 x 20 mL, and the organics dried over sodium sulfate and filtered. Removal of solvents and drying under high vacuum gave the Weinreb amide **S12** as a colorless oil (2.83 g, 19.9 mmol, 96%), which was used without further purification. **FTIR** (neat): 2854, 1619, 1431, 1267, 1194, 1113, 1035, 916, 630 cm$^{-1}$.**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ =5.23-5.20 (m, 1H), 5.05-5.02 (m, 1H), 3.76-3.50 (m, 8H), 1.98-1.93 (m, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 171.34, 140.15, 115.93, 67.07, 20.59. **HRMS ESI** calc. for $C_8H_{13}NaO_2^+$ $[M+Na]^+$: 178.0838, found 178.0839. sf348

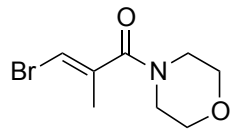
[309] N. K. Rana, V. K. Singh, *Org. Lett.* **2011**, *13*, 6520.

**(*E*)-3-bromo-*N*-methoxy-*N*,2-dimethylacrylamide (3.58):** To a 0 °C cold solution of



Weinreb amide **S11** (2.36 g, 18.3 mmol, 1.0 eq.) in DCM (5 mL) was added drop wise a solution of bromine (950 mL, 18.0 mmol, 1.0 eq.) in DCM (5 mL) and the resulting orange solution was stirred at r.t. for 4 h, after which $^{1}$H NMR indicated complete consumption of the starting material. The mixture was cooled to 0 °C and DBU (4.10 mL, 27.0 mmol, 1.50 eq.) was added drop wise and the resulting dark solution was stirred at r.t. for 15 h, after which TLC indicated complete consumption of the intermediate dibromo species. The dark brown mixture was poured on saturated aqueous sodium thiosulfate solution (10 mL), the organic layer was washed with aqueous HCl (30 mL, 1 M), and the aqueous layers were extracted with DCM (30 mL). Drying over sodium sulfate and removal of solvents gave a brown oil, which appeared pure in $^{1}$H NMR, but not in TLC. It was therefore purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 1:4) to give the title compound **3.58** as a colorless oil (2.20 g, 10.6 mmol, 58%). $\boldsymbol{R_f}$ = 0.35 ($SiO_2$, pentane/$Et_2O$ 1:4). **FTIR** (neat): 2936, 1643, 1370, 1278, 1160, 1027, 821, 715, 684 cm$^{-1}$. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 6.71 (q, *J* = 1.3 Hz, 1H), 3.63 (s, 3H), 3.23 (s, 3H), 2.02 (d, *J* = 1.4 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 168.91, 137.10, 113.01, 61.51, 33.45, 17.69. **HRMS ESI** calc. for $C_6H_{11}BrNO2^+$ $[M+H]^+$: 207.9968, found 207.9968. sf349

**(*E*)-3-bromo-2-methyl-1-morpholinoprop-2-en-1-one (3.59):** To a 0 °C cold solution



of morpholineamide **S12** (2.36 g, 18.3 mmol, 1.0 eq.) in DCM (5 mL) was added drop wise a solution of bromine (950 mL, 18.0 mmol, 1.0 eq.) in DCM (5 mL) and the resulting orange solution was stirred at r.t. for 4h, after which $^{1}$H NMR indicated complete consumption of the starting material. The mixture was cooled to 0 °C and DBU (4.1 mL, 27 mmol, 1.5 eq.) was added drop wise and the resulting dark solution was stirred at r.t. for 15 h, after which TLC indicated complete consumption of the intermediate dibromo species. The dark brown mixture was washed with aqueous HCl (30 mL, 1 M), and the aqueous layer was extracted with DCM (20 mL). Drying over sodium sulfate and removal of solvents gave a brown oil, which was purified by flash chromatography ($SiO_2$, $Et_2O$) to give the title compound **3.59** as a colorless oil (1.21 g, 5.17 mmol, 28%). $\boldsymbol{R_f}$ = 0.40 ($SiO_2$, $Et_2O$). **FTIR** (neat): 2855, 1629, 1428, 1288, 1240, 1113, 1031, 843, 686, 632 cm$^{-1}$. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 6.37 (q, *J* = 1.5 Hz, 1H), 3.71 – 3.62 (m, 5H), 3.60 – 3.43 (m, 4H), 1.99 (d, *J* = 3.2 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ =168.68, 137.30, 110.12,

66.93, 18.12. **HRMS ESI** calc. for $C_8H_{13}BrNO2^+$ $[M+H]^+$: 234.0125, found 234.0124. sf350

***tert*-Butyl 3-hydroxy-2,4-dimethylpent-4-enoate (S13):** The compound was prepared in analogy to a literature procedure.[310] To a 0 °C cold solution of diisopropyl amine (5.09 mL, 36.0 mmol, 1.20 eq.) in THF (20 mL) was added drop wise a solution of *n*-BuLi (21.1 mL, 36.0 mmol, 1.20 eq., 1.6 M in hexane) and the resulting solution was stirred at 0 °C for 30 min, after which the solution was cooled to -70 °C. A solution of *tert*-butyl propionate (4.62 mL, 30.0 mmol, 1.0 eq.) in THF (30 mL) was added *via* a dropping funnel within 10 min and the resulting solution was stirred for 50 min, after which neat acrolein (3.72 mL, 45.0 mmol, 1.50 eq.) was added drop wise. The resulting solution was stirred for 20 min, quenched by addition of saturated aqueous $NH_4Cl$ (80 mL) and separated between water (40 mL) and $Et_2O$ (100 mL). The aqueous layer was extracted with $Et_2O$ (3 x 120 mL) and the combined organic layers were dried over sodium sulfate, filtered and the solvents removed. Flash chromatography ($SiO_2$, pentane/$Et_2O$ 8:1) afforded the title compound **S13** as a colorless oil (5.2 g, 25 mol, 82%) in a 1:1 mixture of diastereoisomers. Analytical data were in full agreement with the literature values. $\boldsymbol{R_f}$ = 0.30 ($SiO_2$, pentane/$Et_2O$ 8:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 4.96 (dddd, J = 19.2, 11.6, 6.0, 4.6 Hz, 1H), 4.34 (d, J = 4.1 Hz, 0.5H), 4.08 (d, *J* = 7.6 Hz, 0.5H), 2.86 (br s, 0.5H), 2.70 (gr s, 0.5H), 2.63 – 2.50 (m, 1H), 1.75 – 1.69 (m, 3H), 1.49 – 1.44 (m, 9H), 1.10 (dd, *J* = 7.2, 1.0 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 175.49, 144.76, 113.63, 43.74, 28.22, 19.08, 17.43, 14.71, 10.71. sf358

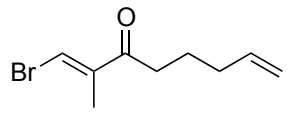
**2,2,5-trimethyl-6-(prop-1-en-2-yl)-4H-1,3-dioxin-4-one (3.52):**[310] To a solution of allylic alcohol **S13** (5.08 g, 24.1 mmol, 1.0 eq.) in DMSO (40 mL) was added IBX (8.50 g, 31.3 mmol,, 1.30 eq.) and the resulting suspension was stirred at r.t. overnight, after which TLC indicated complete consumption of the starting material. The residue was filtered off and the filtrate was diluted with $Et_2O$ (400 mL) and washed with water (4x100 mL). The organic layer was dried over sodium sulfate, filtered and removal of solvent gave *tert*-butyl 2,4-dimethyl-

[310] E. Bourcet, F. Fache, O. Piva, *Tetrahedron* **2010**, *66*, 1319.

3-oxopent-4-enoate (4.69 g, 23.7 mmol, 98%) as a colorless oil, which was used without further purification in the next step. All analytical data were in full agreement with the literature values. $R_f$ = 0.45 ($SiO_2$, pentane/$Et_2O$ 8:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 5.98 (s, 1H), 5.82 (q, *J* = 1.3 Hz, 1H), 4.0 (q, *J* = 7.0 Hz, 1H), 1.90 (d, *J* = 0.7 Hz, 3H), 1.41 (s, 9H), 1.33 (d, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 197.74, 170.46, 144.16, 125.18, 81.62, 77.48, 77.36, 77.16, 76.84, 48.64, 27.96, 18.08, 13.71. sf368

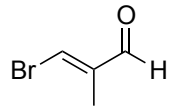
To a 0 °C cold solution of the ester **3.56** (1.0 g, 4.8 mmol, 1.0 eq.) in dry Acetone (1.8 mL, 24 mmol, 5.0 eq.) was added trifluoroacetic anhydride (3.3 mL, 24 mmol, 5.0 eq.) and after 15 min of stirring trifluoroacetic acid (1.8 mL, 24 mmol, 5.0 eq.) was added. The solution was stirred at r.t. for 2 h after which TLC indicated incomplete transformation. Argon was bubbled through the reaction mixture for 20 min, which pushed the reaction to completion. The orange reaction mixture was diluted with $Et_2O$ (70 mL) and washed with saturated aqueous bicarbonate solution (3 x 30 mL). The organic layer was dried over sodium sulfate, filtered and the solvents removed *in vacuo* to give the title compound **3.52** (959 mg, 4.79 mmol, 98%, 91% pure in $Et_2O$) as an orange oil which was used without further purification. $R_f$ = 0.30 ($SiO_2$, pentane/$Et_2O$ 4:1). **FTIR** (neat): 2998, 2942, 1724, 1630, 1358, 1284, 1205, 1148, 968, 919, 633 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 5.44 (dd, *J* = 3.0, 1.5 Hz, 1H), 5.28 (d, *J* = 0.9 Hz, 1H), 1.91 (s, 3H), 1.90 – 1.89 (m, 3H), 1.67 (s, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ =163.55, 162.47, 136.91, 121.64, 104.91, 100.98, 25.0, 19.96, 11.71. **HRMS ESI** calc. for $C_{10}H_{15}O_3^+$ $[M+H]^+$: 183.1016, found 183.1018. sf370

**(*E*)-1-bromo-2-methylocta-1,7-dien-3-one (3.60):** To a suspension of flame dried magnesium turnings (43 mg, 1.8 mmol, 3.7 eq.) in dry THF (1 mL) was added a solution of 5-Bromo-1-pentene (200 mL, 1.7 mmol, 3.5 eq.) in dry THF (1.5 mL). The solution became warm and turbid, and after it had reached r.t. again (ca. 30 min), it was cannulated to a -70 °C cold solution of the Weinreb amide **3.58** (100 mg, 184 mmol, 1.0 eq.) in dry THF (0.5 mL). The solution was stirred for 10 min and then warmed to -30 °C, upon which TLC indicated formation of product. The greenish solution was stirred for 1 h and was then quenched by addition of saturated aqueous $NH_4Cl$ (4 mL). The layers were separated, the aqueous layer was extracted with $Et_2O$ (3 x 5 mL) and the unified organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography ($SiO_2$, pentane/$Et_2O$ 50:1) afforded the title compound **3.60** as a



colorless oil (30.0 mg, 138 mmol, 29%). $R_f$ = 0.40 ($SiO_2$, pentane/$Et_2O$ 50:1). **FTIR** (neat): $\tilde{\nu}$ = 2933, 1677, 1601, 1369, 1290, 1185, 1043, 913, 729, 660 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.47 (q, *J* = 1.3 Hz, 1H), 5.77 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.08 – 4.96 (m, 2H), 2.68 – 2.60 (m, 2H), 2.08 (q, *J* = 7.1 Hz, 3H), 1.73 (p, *J* = 7.4 Hz, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 197.86, 143.06, 137.98, 123.53, 115.58, 37.39, 33.18, 23.46, 15.27. **HRMS ESI** calc. for $C_9H_{13}BrNaO^+$ $[M+Na]^+$: 239.042, found 239.041. sf376 sf372

**(*E*)-3-bromo-2-methylacrylaldehyde (3.64):**[311] To a 0 °C cold solution of methyl methacrylate (21.3 mL, 200 mmol, 1.0 eq.) in DCM (40 mL, 5M) was slowly added a solution of bromine (10.4 mL, 200 mmol, 1.0 eq.) in DCM (20 mL, 10 M) *via* a dropping funnel. After stirring at r.t. for 4 h, DBU (54 ml 300 mmol, 1.50 eq.) was added *via* a dropping funnel, upon which the solution turned from brown orange to bright yellow. The mixture was stirred overnight, poured on aqueous HCl (200 mL 1 M) and the separated aqueous layer was extracted with $Et_2O$ (3 x 70 mL) The unified organic layers were dried over sodium sulfate and concentrated *in vacuo* to yield pure (*E*)-methyl 3-bromo-2-methylacrylate (32.5 g, 198 mmol, 99%), which was used without further purification in the next step. All analytical data were in full agreement with the literature. **$^1$H NMR** (400 MHz, $CDCl_3$) δ =7.52 (q, *J* = 1.4 Hz, 1H), 3.76 (s, 3H), 2.0 (d, *J* = 1.5 Hz, 3H).




To a 0 °C cold stirred suspension of $LiAlH_4$ (7.14 g, 198 mmol, 1.0 eq.) in dry $Et_2O$ (300 mL, 0.6 M) was added *drop wise* a solution of (*E*)-methyl 3-bromo-2-methylacrylate (32.5 g, 198 mmol, 1.0 eq.) in dry $Et_2O$ (100 mL, 1.9M) *via* a dropping funnel. The mixture was stirred at r.t. for 1h, after which TLC indicated complete consumption of the starting material. MeOH (12 mL) was added *drop wise* (!) until bubbling ceased, then water (8 mL) was added followed by aqueous NaOH (8 mL, 4 M) and finally water (25 mL). The mixture was stirred until a white precipitate had formed, which was filtered off. Removal of the solvent under rotary evaporation at 500 mbar and 40 °C gave the (*E*)-3-bromo-2-methylprop-2-en-1-ol (37.3 g, 160 mmol, 85%) as a 64% w/w solution in $Et_2O$, which was used without further purification in the next step. The compound was stored preferably at this stage, as the corresponding aldehyde

[311] X. Li, X. Zeng, *Tetrahedron Lett.* **2006**, *47*, 6839; Y. Murakami, M. Nakano, T. Shimofusa, N. Furuichi, S. Katsumura, *Org. Biomol. Chem.* **2005**, *3*, 1372.

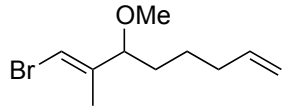
decomposes. All analytical data were in full agreement with the literature. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.26 – 6.23 (m, 1H), 4.09 (s, 2H), 1.82 (d, *J* = 0.5 Hz, 3H).

To a solution of (*E*)-3-bromo-2-methylprop-2-en-1-ol (2.52 g, 60% w/w in $Et_2O$, 10.0 mmol, 1.0 eq.) in DCM (30 mL) was added activated $MnO_2$ (9.56 g, 110 mmol, 11.0 eq., oven-dried at 120 °C) and the black suspension was stirred at r.t. After 18 h TLC indicated incomplete conversion and $MnO_2$ (4.0 eq.) was added. After 36 h TLC indicated complete conversion and the suspension was filtered over diatomaceous earth and concentrated by rotary evaporation (630 mbar, 40 °C) to give the title compound **3.64** (7.5 g, 20% w/w in DCM, 10.0 mmol, quant.). The compound partially decomposes within 2–3 weeks at 5 °C, and even faster when stored neat. A colorless precipitate and browning of the solution is then observed, but a filtration can yield again sufficiently pure aldehyde for the Grignard reaction according to $^1$H NMR. For Grignard reactions, the DCM was removed prior to the reaction by rotary evaporation (200 mbar, 40 °C). All analytical data were in full agreement with the literature. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.49 (s, 1H), 7.44 (dd, *J* = 2.6, 1.3 Hz, 1H), 1.90 (d, *J* = 1.3 Hz, 3H).

**(*E*)-1-bromo-2-methylocta-1,7-dien-3-ol (S14):** To a suspension of flame dried magnesium turnings (147 mg, 6.04 mmol, 2.2 eq.) in dry THF (4.0 mL) was added a solution of 5-bromo-1-pentene (0.65 mL, 5.5 mmol, 2.0 eq.) in dry THF (2.0 mL). The solution became warm and turbid, and after it had reached r.t. again (ca. 30 min), it was cannulated to a -70 °C cold solution of the aldehyde **3.64** (409 mg, 2.75 mmol, 1.0 eq.) in dry THF (4.0 mL). The grey suspension was stirred for 30 min and then stirred at r.t. for 20 min, upon which TLC indicated complete consumption of the aldehyde. The greenish solution was then quenched by addition of saturated aqueous $NH_4Cl$ (10 mL). The layers were separated, the aqueous layer was extracted with $Et_2O$ (3 x 10 mL) and the unified organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography ($SiO_2$, pentane/$Et_2O$ 4:1) afforded the title compound **S14** as a colorless oil (433 mg, 1.98 mmol, 72%). $\boldsymbol{R_f}$ = 0.25 ($SiO_2$, pentane/$Et_2O$ 4:1). **FTIR** (neat): 2862, 1639, 1290, 996, 911, 632 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.23 (dt, *J* = 2.1, 1.2 Hz, 1H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.05 – 4.94 (m, 2H), 4.13 (td, *J* = 6.5, 2.8 Hz, 1H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.78 (d, *J* = 0.9 Hz, 3H), 1.62 – 1.54 (m, 4H), 1.52 – 1.42 (m, 1H), 1.41 – 1.30 (m, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 144.07, 138.48,

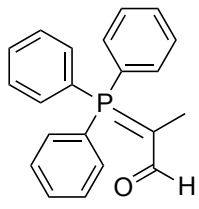
115.07, 104.75, 76.15, 34.37, 33.60, 24.90, 14.93. **HRMS ESI** calc. for $C_9H_{15}BrNaO^+$ $[M+Na]^+$: 241.0198, found 241.0200. sf381 sf384

**(*E*)-1-bromo-3-methoxy-2-methylocta-1,7-diene (3.53):** To a 0 °C solution of the




alcohol **S14** (342 mg, 1.48 mmol, 1.0 eq.) in dry THF (5.0 mL) was added NaH (297 mg, 7.41 mmol, 5.0 eq., 60% dispersion in mineral oil) and after 2 min methyl iodide (0.55 mL, 8.9 mmol, 6.0 eq.). After 10 min, the solution was stirred at r.t. for 20 min, after which TLC indicated complete consumption of the starting material. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (9 mL) and was then diluted with water (10 mL) and $Et_2O$ (20 mL). The layers were separated, the aqueous layer was extracted with $Et_2O$ (3 x 15 mL) and the unified organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residual mineral oil was removed by filtration with pentane over a silica plug and washing off the title compound **3.53** with pentane/$Et_2O$ (4:1) to give a colorless oil (350 mg, 1.50 mmol, 100%). The compound could not be ionized by our available LCMS ESI or HRMS ESI methods. $\boldsymbol{R_f}$ = 0.20 ($SiO_2$, pentane). **FTIR** (neat): 2942, 1640, 1459, 1285, 1099, 911, 717, 607 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.15 (dd, *J* = 1.2, 0.5 Hz, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.93 (m, 2H), 3.57 – 3.51 (m, 1H), 3.20 (d, *J* = 3.6 Hz, 3H), 2.05 (q, *J* = 7.1 Hz, 2H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.68 – 1.57 (m, 2H), 1.54 – 1.38 (m, 2H), 1.36 – 1.25 (m, 2H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 141.89, 138.59, 114.94, 105.0, 85.44, 77.48, 77.36, 77.16, 76.84, 56.44, 33.67, 33.13, 25.08, 14.05. sf385 sf387

**2-(triphenylphosphoranylidene)propanal (S15):**[312] A 20 mL microwave vial with a



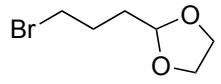

stirring bar was charged with triphenyl phosphine (7.8 g, 30 mmol, 1.0 eq.) and iodoethane (2.4 mL, 30 mmol, 1.0 eq.), sealed and heated to 150 °C for 4h in a microwave reactor. Precipitation from pentane/$Et_2O$ (1:1 *v*/*v*) gave ethyltriphenylphosphonium iodide (13 g, 30 mmol,

[312] M. Engman, P. Cheruku, P.Tolstoy, J. Bergquist, S. F. Völker, P. G. Andersson, *Adv. Synth. Catal.* **2009**, *351*, 375; Kiyooka, S.-I.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511.

99%) as a colorless solid. All analytical data were in full agreement with the literature. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.86 – 7.76 (m, 9H), 7.75 – 7.67 (m, 6H), 3.77 (dq, *J* = 12.4, 7.5 Hz, 2H), 1.39 (dt, *J* = 20.0, 7.5 Hz, 3H).

To a solution of ethyltriphenylphosphonium iodide (1.0 g, 2.39 mmol, 1.0 eq.) in dry THF (7.2 mL 0.3 M) was added *n*-BuLi (1.64 mL, 2.63 mmol, 1.1 eq., 1.6 M in hexane) at r.t. and a dark red solution formed, which was stirred for 30 min before being cooled to 0 °C in an ice bath. KO*t*Bu (2.63 mL, 2.63 mmol, 1.1 eq. 1.0 M in THF) and neat ethyl formate (0.5 mL, 6.0 mmol, 2.5 eq.) were added in quick succession, and the dark brown solution was stirred at 0 °C for 15 min before being diluted with DCM (7 mL) and quenched by addition of aqueous HCl (3 mL, 1 M, 1.25 eq.). The pH was adjusted to 7–8 with aqueous NaOH (2 M) when necessary. The biphasic mixture was stirred for 30 min and the layers were separated. The aqueous layer was extracted with DCM (10 mL) and the yellow organic layer was dried over sodium sulfate, filtered and the solvent removed to give the title compound **S15** as an amorphous yellow sticky solid (737 mg, 2.32 mmol, 97%) of sufficient purity for further reactions which was stored at -20 °C. All analytical data were in full agreement with the literature. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 5.0 Hz, 1H), 7.70 – 7.52 (m, 15H), 1.87 (d, *J* = 13.5 Hz, 3H). sf420 sf518

**2-(3-bromopropyl)-1,3-dioxolane (3.69):**[313] To a -70 °C cold solution of ethyl-4-bromobutyrate **3.68** (3.9 g, 20 mmol, 1.0 eq.) in DCM (40 mL) was added a solution of DIBAL-H (4.3 mL, 21 mmol, 1.05 eq., 1.1 M in cyclohexane) *via* transfer cannula. The solution was stirred for 1 h and the poured on ice cold aqueous HCl (60 m, 3M) and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with DCM (3 x 30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure (630 mbar, 40 °C). The obtained colorless oil (10 g) was used directly in the next step without further purification.

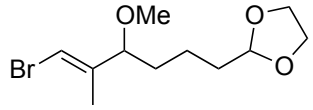



To a solution of crude aldehyde (3.0 g, 20 mmol, 1.0 eq.) in toluene (60 mL) was added ethylene glycol (8.39 mL, 150 mmol, 7.50 eq.) and *p*-toluenesulfonic acid (152 mg, 800 mmol, 4 mol%). The mixture was heated to reflux with a Dean-Stark trap attached overnight, after which $^1$H NMR indicated complete consumption of the aldehyde. The

[313] G. N. Varseev, M. E. Maier, M. E. *Org. Lett.* **2005**, *7*, 3881.

mixture was quenched with $NaHCO_3$ (800 mg), extracted with saturated aqueous $NaHCO_3$ (40 mL), dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The crude colorless oil (4.5 g) was purified by fractional distillation to yield the title compound **3.69** (1.93 g, 10.6 mmol, 51% over two steps) as a colorless oil. All analytical data were in full agreement with the literature. **B.p.**: 71 °C, 14 mbar. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 4.90 (t, *J* = 4.5 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.90 – 3.81 (m, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 2.06 – 1.96 (m, 2H), 1.86 – 1.79 (m, 2H). sf411

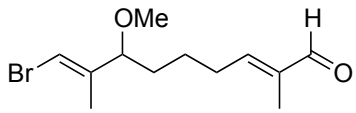
**(*E*)-2-(6-bromo-4-methoxy-5-methylhex-5-en-1-yl)-1,3-dioxolane (S16):** To a suspension of freshly ground and oven dried magnesium turnings (127 mg, 5.23 mmol, 1.70 eq.) in dry THF (2.5 mL) was added a solution of 2-(3-bromopropyl)-1,3-dioxolane **3.69** (1.0 g, 4.6 mmol, 1.5 eq.) in THF (2.5 mL) in one portion. The mixture began to reflux quickly and the resulting grey suspension was stirred for 30 min, after which it was transferred *via* cannula to a 0 °C solution of aldehyde **3.64** (2.30 g of a 20% solution in DCM, 3.08 mmol, 1.0 eq.) in THF (3.0 mL). The yellow mixture was stirred for 1 h at r.t. before being quenched with saturated aqueous $NH_4Cl$ (8 mL), diluted with ether (10 mL) and the separated aqueous layer was extracted with ether (3 x 10 mL). The unified organic layers were dried over sodium sulfate, filtered, and the solvents removed to give a colorless oil (950 mg), which was used without further purification in the next step. The neat oil decomposed at 5 °C within 12 h. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.23 (s, 1H), 4.85 (t, *J* = 4.7 Hz, 1H), 4.13 (t, *J* = 6.5 Hz, 1H), 4.01 – 3.93 (m, 2H), 3.92 – 3.81 (m, 2H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.74 – 1.58 (m, 6H).




The crude alcohol (950 mg, 3.08 mmol, 1.00 eq.) was dissolved in dry THF (9.0 mL, 0.3 M), cooled to 0 °C, and sodium hydride (370 mg, 9.24 mmol, 3.0 eq., 60% in mineral oil) was added. After stirring for 10 min, methyl iodide (0.80 mL, 12.3 mmol, 4.0 eq.) was added and stirring was continued for 10 min at 0 °C and 20 min at r.t.. The yellow mixture was *carefully* quenched with saturated aqueous $NH_4Cl$ (4 mL), diluted with ether (10 mL) and the separated aqueous layer was extracted with ether (3 x 10 mL). The unified organic layers were dried over sodium sulfate, filtered, and the solvents removed to give a colorless oil (950 mg). The mineral oil was washed off by filtration over a silica plug with pentane (50 mL) before the product was eluted with $Et_2O$/pentane (1:1 *v*/*v*, 50 mL). Removal of solvents gave the methylated alcohol **S16** (708 mg, 279 mmol, 91%) as a colorless oil. $\boldsymbol{R_f}$ = 0.35 ($SiO_2$, pentane/$Et_2O$ 4:1). **$^1$H NMR** (400 MHz,

$CDCl_3$) δ = 6.14 (q, *J* = 2.4 Hz, 1H), 4.83 (t, *J* = 4.8 Hz, 1H), 4.03 – 3.90 (m, 2H), 3.90 – 3.80 (m, 2H), 3.55 – 3.51 (m, 1H), 3.18 (s, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.65 – 1.33 (m, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 141.75, 105.12, 104.52, 85.41, 64.99, 56.44, 33.75, 29.58, 24.10, 20.42, 14.04.

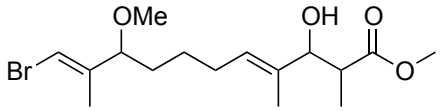
**(2*E*,8*E*)-9-bromo-7-methoxy-2,8-dimethylnona-2,8-dienal** (**S17**)**:** A 5 mL microwave reactor vial was charged with the dioxolane **S16** (200 mg, 612 mmol, 1.0 eq.) and *p*-TsOH•$H_2O$ (13.0 mg, 61.2 mmol, 10 mol%) and suspended in a mixture of acetone/$H_2O$ (2.5 mL, 3:1 *v*/*v*). The suspension was heated to 100 °C for 40 min, diluted with $Et_2O$ (8 mL) and extracted with half saturated aqueous $Na_2CO_3$ (2 x 4 mL). Drying over sodium sulfate, filtration and evaporation gave the crude aldehyde **S18** (180 mg, 612 mmol, 80% w/w pure, 90%) together with unreacted starting material (20% w/w). Prolonged reaction time or higher amount of acid catalyst did not improve the conversion. The compounds were inseparable by flash chromatography. The crude mixture was used without further purification in the next step. $\boldsymbol{R_f}$ = 0.40 ($SiO_2$, pentane/$Et_2O$ 4 :1) **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.76 (t, *J* = 1.5 Hz, 1H), 6.17 (s, 1H), 3.55 (t, *J* = 6.3 Hz, 1H), 3.19 (s, 3H), 2.45 (dt, *J* = 6.9, 3.5 Hz, 2H), 1.71 (d, J = 1.2 Hz, 3H), 1.68 – 1.61 (m, 4H). Sf422




The crude aldehyde **S18** (400 mg, 75% pure, 1.28 mmol, 1.00 eq.) was dissolved in a dry mixture of toluene/DCM (2:1 *v*/*v*, 0.2 M final conc.) and the flask equipped with a reflux condenser. Phosphorane **S15** (450 mg, 1.28 mmol, 1.00 eq.) was added and the mixture was stirred in a sand bath at 65 °C for 24 h, upon which $^1$H NMR indicated a ratio product/starting material of ca. 4:5 in the crude brown mixture. Phosphorane **S15** (450 mg, 1.28 mmol, 1.00 eq.) was added and stirring for another 24 h provided a mixture of ca. 2:1 product/starting material as determined by $^1$H NMR (further addition of phosphorane and prolonged stirring does not increase the ratio and byproduct formation was observed). The solvents were removed and the crude brown oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 4:1) to provide the unsaturated aldehyde **S17** (252 mg, 70% pure w/w, 640 mmol, 50%, *E*/*Z* >20:1) with ca. 30% w/w of unreacted dioxolane **S16** as an impurity. $\boldsymbol{R_f}$ = 0.30 ($SiO_2$, pentane/$Et_2O$ 4:1). **FTIR** (neat): 2932, 2865, 1686, 1450, 1285, 1097, 715 cm$^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.39 (s, 1H), 6.46 (td, *J* = 7.4, 1.3 Hz, 1H), 6.17 (d, *J* = 0.8 Hz, 1H), 3.55 (dd, *J* = 7.2,

5.6 Hz, 1H), 3.19 (s, 3H), 2.36 (q, *J* = 7.2 Hz, 2H), 1.74 (d, *J* = 0.9 Hz, 3H), 1.71 (t, *J* = 1.6 Hz, 4H), 1.68 – 1.42 (m, 4H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 195.35, 154.07, 141.61, 139.81, 105.30, 85.20, 56.48, 33.40, 28.87, 24.76, 14.09, 9.38. **HRMS ESI** calc. for $C_{12}H_{19}BrNaO_2^+$ $[M+Na]^+$: 297.0461, found 297.0459. sf423 sf426

**(4*E*,10*E*)-methyl 11-bromo-3-hydroxy-9-methoxy-2,4,10-trimethylundeca-4,10-dienoate 3.71:** To a 0 °C cold solution of diisopropyl amine (120 mg, 1.19 mmol, 1.80 eq.) in THF (1.0 mL) was added drop wise a solution of *n*-BuLi (703 mL, 1.12 mmol, 1.70 eq., 1.6 M in hexanes) and the mixture was stirred for 20 min before being cooled to -70 °C. A solution of methyl propionate (87 mg, 99 mmol, 1.5 eq.) in THF (1.0 mL) was added to the LDA solution via transfer cannula, and the mixture was stirred for 30 min at -70 °C before a solution of the aldehyde **S17** (260 mg, 661 mmol, 1.00 eq., 70% w/w pure) in THF (1.0 mL) was added slowly drop wise. The yellow mixture was stirred for 40 min before saturated aqueous $NH_4Cl$ (3 mL) was added, diluted with $Et_2O$ (5 mL) and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The unified organic layers were dried over sodium sulfate, filtered, and the solvents removed to give a yellow oil (330 mg). The crude oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 3:2) to provide the b-hydroxy ester **3.71** (180 mg, 470 mmol, 71%) as a mixture of partially separable diastereomers (ca. 2:1). Analytical data is given for the major diastereomer. $\boldsymbol{R_f}$ = 0.20 ($SiO_2$, pentane/$Et_2O$ 3:2). **FTIR** (neat): 3459 (br), 2938, 1737, 1454, 1346, 1251, 1163, 1049, 1026, 798, 714 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.13 (q, *J* = 1.2 Hz, 1H), 5.40 (t, *J* = 7.1 Hz, 1H), 4.06 (d, *J* = 9.0 Hz, 1H), 3.70 (s, 3H), 3.52 (t, *J* = 6.7 Hz, 1H), 3.17 (s, 3H), 2.68 – 2.60 (m, 1H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.58 (d, *J* = 0.6 Hz, 3H), 1.50 – 1.35 (m, 3H), 1.32 – 1.22 (m, 2H), 1.01 (d, *J* = 7.1 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 176.50, 141.64, 134.46, 129.27, 104.92, 85.21, 79.93, 56.20, 51.79, 43.06, 33.18, 27.25, 25.45, 14.32, 13.74. **HRMS ESI** calc. for $C_{16}H_{27}BrNaO_4^+$ $[M+Na]^+$: 385.0985, found 385.0985. sf427 sf428



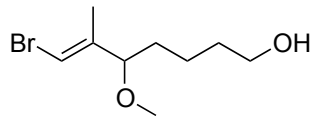
**(4-bromobutoxy)triethylsilane (3.75):**[314] A dry 50 mL round bottom flask under an argon atmosphere equipped with a reflux condenser was charged with triethylsilane (5.34 mL, 33.5 mmol, 1.0 eq.), THF (4.22 mL, 51.5 mmol, 1.54 eq.) and freshly distilled allyl bromide (7.57 mL, 87.0 mmol, 2.60 eq.) in this order. To the stirred mixture was added palladium(II) chloride (102 mg, 569 mmol, 1.7 mol%). The palladium(II) chloride *must* (!) be added last or rapid decomposition and boiling of the solution ensues! The solution began to reflux and was maintained at 70 °C for 18h, after which the volatiles were removed by rotary evaporation. Fractional distillation gave the title compound **3.75** as a colorless oil (6.69 g, 25.4 mmol, 76%). In some cases redistillation of some fractions had to be conducted. All analytical data were in full agreement with the literature. **B.p.**: 79 °C, 1.4 mbar. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 3.64 (t, *J* = 6.2 Hz, 2H), 3.45 (t, *J* = 6.8 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.71 – 1.62 (m, 2H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H).

**(*E*)-1-bromo-2-methyl-7-((triethylsilyl)oxy)hept-1-en-3-ol (S19):** To a suspension of freshly ground oven dried magnesium turnings (157 mg, 6.47 mmol, 1.7 eq.) in dry THF (3.5 mL) in a round bottom flask equipped with a small reflux condenser was added a solution of alkyl bromide **3.75** (1.60 g, 5.71 mmol, 1.50 eq.) in dry THF (3.5 mL). The suspension started to reflux and turned greyish-black after 15 min and was stirred at r.t. for 40 min total, after which no more dissolving of magnesium and warming was observed. This Grignard solution (ca. 1 M) was transferred *via* cannula to a 0 °C cold solution of aldehyde **3.64** (567 mg, 3.81 mmol, 1.00 eq.) in THF (8 mL, 0.5 M), upon which the mixture turned dark yellow. The mixture was stirred for 2 h at r.t., after which $^1$H NMR indicated complete consumption of the aldehyde. Saturated aqueous $NH_4Cl$ (8 mL) was added, then the mixture was diluted with $Et_2O$ (10 mL) and the separated aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The unified organic layers were dried over sodium sulfate, filtered, and the solvents removed to give a yellow-greenish oil. The crude oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 4:1) to provide the alcohol **S19** (870 mg, 2.56 mmol, 68%) as a slightly

[314] J. Ohshita, A. Iwata, F. Kanetani, A. Kuna, *J. Org. Chem*. **1999**, *64*, 8024.

yellow oil. The neat alcohol should be used immediately and not be stored longer than 1–2 weeks at 5°C, as significant decomposition is observed in the $^1$H NMR. $\boldsymbol{R_f}$ = 0.30 ($SiO_2$, pentane/$Et_2O$ 4:1). **FTIR** (neat): 3377 (br), 2950, 2876, 1459, 1289, 1096, 1005, 660 cm$^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.24 – 6.22 (m, 1H), 4.13 (t, *J* = 6.5 Hz, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.63 – 1.50 (m, 4H), 1.47 – 1.27 (m, 2H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 144.06, 104.70, 76.23, 62.81, 34.72, 32.60, 22.11, 14.95, 6.93, 4.54. **HRMS ESI** calc. for $C_{14}H_{29}BrNaO_2Si^+$ $[M+Na]^+$: 359.1012, found 359.1012. sf433

**(*E*)-7-bromo-5-methoxy-6-methylhept-6-en-1-ol (S20):** To a 0 °C cold solution of the alcohol **S19** (220 mg, 652 mmol, 1.0 eq.) in dry THF (2 mL, 0.3 M) was added sodium hydride (78 mg, 2.0 mmol, 3.0 eq., 60% dispersion in mineral oil). After stirring for 10 min, MeI (160 mL, 2.61 mmol, 4.0 eq.) was added and the suspension was stirred for 30 min, after which TLC indicated complete consumption of the starting material. The mixture was cooled to 0 °C and saturated aqueous $NH_4Cl$ (4 mL) was added, then the mixture was diluted with $Et_2O$ (10 mL) and water (4 mL), and the separated aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The unified organic layers were dried over sodium sulfate, filtered, and the solvents removed to give a colorless oil (230 mg, 622 mmol , 95%) which was used without further purification in the next step. $\boldsymbol{R_f}$ = 0.85 ($SiO_2$, pentane/$Et_2O$ 4:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.14 (s, 1H), 3.59 (t, *J* = 6.7 Hz, 2H), 3.54 (t, *J* = 6.8 Hz, 1H), 3.19 (s, 3H), 1.70 (s, 3H), 1.65 – 1.46 (m, 4H), 1.38 – 1.19 (m, 2H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H). sf442




The crude alcohol (230 mg, 622 mmol, 1.0 eq.) was dissolved in dry THF (1 mL) and TBAF (690 mL, 690 mmol, 1.05 eq., 1.0 M solution in THF) was added. After 1h TLC indicated complete consumption of the starting material and saturated aqueous $NH_4Cl$ (4 mL) was added, then the mixture was diluted with $Et_2O$ (5 mL) and the separated aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The unified organic layers were dried over sodium sulfate, filtered, and the solvents removed to give a colorless oil. The crude oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 1:1) to provide the alcohol **S20** (115 mg, 475 mmol, 73%) as a colorless oil. $\boldsymbol{R_f}$ = 0.20 ($SiO_2$, pentane/$Et_2O$ 1:1). **FTIR** (neat): 3380, 2934, 1631, 1450, 1286, 1087, 905, 79, 714 cm$^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.15 (s, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.55 (dd, *J* = 7.0, 6.3 Hz, 1H), 3.19 (s, 3H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.68 – 1.27 (m, 8H).**$^{13}$C NMR** (101 MHz,

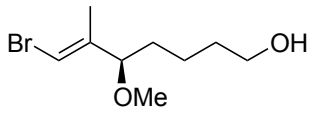
$CDCl_3$) δ = 141.66, 104.97, 85.36, 62.77, 56.31, 33.32, 32.50, 21.95, 13.91. **HRMS ESI** calc. for $C_9H_{17}BrNaO_2^+$ $[M+Na]^+$: 259.0304, found 259.0302. sf443

**(*E*)-7-bromo-5-methoxy-6-methylhept-6-enal (3.70):** To a solution of the alcohol **S20** (100 mg, 422 mmol, 1.0 eq.) in DMSO (1 mL) was added IBX (177 mg, 633 mmol, 1.5 eq.). After 2 h a white suspension had formed and TLC/$^1$H NMR indicated complete consumption of the starting material. The mixture was diluted with $Et_2O$ (10 mL) and extracted with water (5 mL) and saturated aqueous $Na_2CO_3$ (2 x 5 mL), where the colorless precipitate stays mainly in the organic layer. The organic layer was dried, filtered and evaporated, dissolved in $Et_2O$ and filtered over cotton in a Pasteur pipette to remove the colorless precipitate. The product **3.70** was obtained as a colorless oil (90 mg, 0.38 mmol, 90%) after evaporation. $R_f$ = 0.50 ($SiO_2$, pentane/$Et_2O$ 1:1). **FTIR** (neat): 2932, 1708, 1631, 1286, 1101, 941, 794, 715. $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.76 (t, *J* = 1.6 Hz, 1H), 6.17 (qd, *J* = 1.4, 0.6 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.19 (s, 3H), 2.49 – 2.42 (m, 2H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.68 – 1.48 (m, 6H).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 202.25, 141.54, 105.39, 85.16, 56.46, 43.72, 33.15, 18.50, 14.11. **HRMS ESI** calc. for $C_{10}H_{19}BrNaO_3^+$ $[M+Na]^+$: 289.0410, found 289.0408. sf444

**(*E*)-1-bromo-2-methyl-7-((triethylsilyl)oxy)hept-1-en-3-one (S21)**: The racemic allylic alcohol **S19** (1.28 g, 3.63 mmol, 1.0 eq.) was dissolved in dry DCM (12 mL) and NMO (638 mg, 5.54 mmol, 1.5 eq.) and powdered molecular sieves (4 Å, 800 mg) were added. The stirring suspension was cooled to 0 °C and TPAP (63.8 mg, 182 mmol, 5 mol%) was added. The reaction was monitored by TLC (pentane/$Et_2O$ 4:1) and was found to have stalled after 30 min (addition of more catalyst can drive the reaction to quantitative conversion, but none was available. Chromatography can then be replaced by filtration over a silica plug with DCM). The dark green-black reaction mixture was therefore concentrated and the crude slurry was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 4:1) to give the product **S21** (867 mg, 2.59 mmol, 71%, 91% brsm) and starting material **S19** (247 mg, 732 mmol, 20%). The alcohol was directly used in the next step, as it decomposes overnight at 5 °C. All attempts to measure an ESI-HRMS had failed, as the sample had already decomposed before measurement. $R_f$ = 0.70 ($SiO_2$, pentane/$Et_2O$ 4:1). **FTIR** (neat): $\tilde{\nu}$ = 2926, 2360, 1680,

1375, 1236, 1071 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.48 (dd, *J* = 2.6, 1.2 Hz, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.70 – 2.65 (m, 2H), 1.96 (d, *J* = 1.3 Hz, 3H), 1.73 – 1.64 (m, 2H), 1.59 – 1.49 (m, 2H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 198.0, 143.0, 123.55, 62.61, 38.09, 32.35, 29.86, 21.17, 15.26, 6.93, 6.73, 5.95, 4.55. sf477

**(*R*,*E*)-7-bromo-5-methoxy-6-methylhept-6-en-1-ol (S22):** The labile bromo-enone



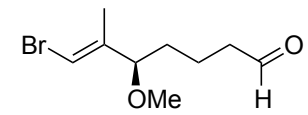

**S21** (860 mg, 2.56 mmol, 2.0 eq.) was dissolved in dry toluene (13 mL) and (*S*)-CBS catalyst (213 mg, 768 mmol, 0.3 eq.) was added. The stirring reaction was cooled to -70 °C and borane dimethyl sulfide complex (2.56 mL, 5.12 mmol, 2.0 eq., 2 M in THF) was added slowly. The reaction was stirred for 15 min, warmed to -35 °C, stirred for 30 min and then stirred at 0 °C. After 2h TLC indicated complete consumption of the starting material, and MeOH (5 mL) was added *carefully* to the reaction mixture. The colorless solution was diluted with $Et_2O$ (40 mL), washed with water (3 x 10 mL) and dried over sodium sulfate. Upon filtration and removal of solvent a crude colorless oil (950 mg, 2.81 mmol, 104%) was obtained. All analytical data were in full agreement with the racemic compound **S19**. The crude labile (!) allylic alcohol was directly used in the next step. **e.r.** = 98:2 (determined with chiral HPLC; Chiralpak OD-H, heptane/isopropanol 99:1, 1.0 mL/min, injection vol.: 1 μL, 25 °C, $t_R$ (*S*): 7.98 min, $t_R$ (*R*): 8.59 min. sf473 sf478 sf523

The crude alcohol (860 mg, 2.55 mmol, 1.0 eq.) was dissolved in dry THF (9.0 mL, 0.3 M), cooled to 0 °C and sodium hydride (306 mg, 7.65 mmol, 3.0 eq., 60% dispersion in mineral oil) was added. After stirring for 10 min, methyl iodide (0.64 mL, 10.2 mmol, 4.0 eq.) was added and stirring was continued for 10 min at 0 °C and 1 h at r.t., upon which TLC indicated complete consumption of the starting material. The yellow mixture was quenched *carefully* by drop wise addition of MeOH (2 mL), diluted with ether (20 mL) and the separated aqueous layer was extracted with ether (2 x 10 mL). The unified organic layers were dried over sodium sulfate, filtered and the solvents removed to give a crude yellow oil. The mineral oil was removed by filtration over a silica plug, first washing with 50 mL pentane and then the product was eluted with $Et_2O$/pentane (50 mL 1:1 *v*/*v*). Removal of the solvents gave the methylated alcohol **S22** (783 mg, 2.23 mmol, 87% over two steps) as a colorless oil. All analytical Data were identical with the

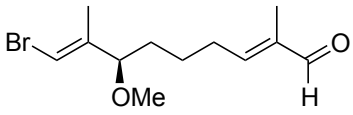
racemic compound. An analytical sample for optical rotation measurement was obtained by flash chromatography ($SiO_2$, pentane/$Et_2O$ 20:1). $[\alpha]_D$ = +23.5 (*c* = 0.34 $CHCl_3$). $R_f$ = 0.45 ($SiO_2$, pentane/$Et_2O$, 20:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.15 – 6.13 (m, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.54 (t, *J* = 6.8 Hz, 1H), 3.19 (s, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.66 – 1.47 (m, 2H), 1.39 – 1.25 (m, 2H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.8 Hz, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 141.85, 105.02, 85.53, 62.83, 56.43, 33.46, 32.81, 22.14, 14.0, 6.93, 4.56. sf479

The crude methyl ether (759 mg, 2.16 mmol, 1.0 eq.) was dissolved in dry THF (8 mL, 0.27 M) and cooled to 0 °C, upon which TBAF (2.37 ml, 2.37 mmol, 1.1 eq., 1.0 M in THF) was added. The reaction was warmed to r.t. and stirred for 30 min, upon which TLC indicated complete consumption of the starting material. The solution was diluted with $Et_2O$ (20 mL) and washed with water (10 mL), dried over sodium sulfate, filtered and the solvents removed. Flash chromatography ($SiO_2$, pentane/$Et_2O$ 3.5:1.5) gave the title compound **S22** (480 mg, 2.02 mmol, 94%) as a colorless oil. All analytical data were in full agreement with the racemic compound **S20**. $[\alpha]_D$ = +9.6 (*c* = 1.05 $CHCl_3$). sf480

**(*R*,*E*)-7-bromo-5-methoxy-6-methylhept-6-enal (3.78)**: The compound was prepared in analogy to the procedure of the racemic compound **3.70**. All analytical data were in full agreement. $[\alpha]_D$ = + 21 (*c* = 0.28 $CHCl_3$). sf484

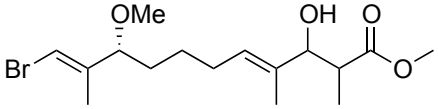



**(*R*,2*E*,8*E*)-9-bromo-7-methoxy-2,8-dimethylnona-2,8-dienal (S23):** To a solution of the aldehyde **3.78** (3.27 g, 13.2 mmol, 1.0 eq.) in dry benzene (32 mL) and DCM (3 mL) was added phosphorane **S15** (4.87g, 14.5 mmol, 1.1 eq.) and the mixture was heated to 90 °C for 18 h, after which $^1$H NMR indicated a ratio of product/ starting material of 5:4. More phosphorane **S15** (0.50 eq.) was added and the mixture was heated to 90 °C for 3 h, after which more phosphorane **S15** (0.50 eq., 2.10 eq. total) was added and the mixture was heated at 90 °C. After 24 h total heating time $^1$H NMR indicated complete consumption of the starting material. The solvents were removed *in vacuo* and the remaining brown oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 3.5:1.5) to give the title compound **S23** (3.44 g, 13.2 mmol, 95%) as a slightly yellow oil. All analytical data

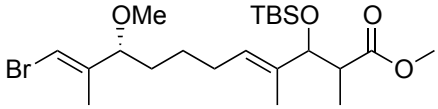


were in full agreement with the racemic compound **S17**. $[\alpha]_D$ = +13.8 (*c* = 0.27, $CHCl_3$). Sf530

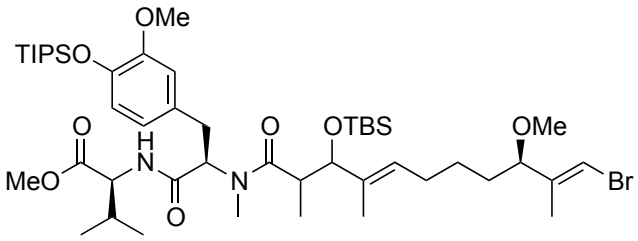
**(4*E*,9*R*,10*E*)-methyl 11-bromo-3-hydroxy-9-methoxy-2,4,10-trimethylundeca-4,10-dienoate (3.79)**: The compound was prepared in analogy to the procedure of the racemic compound **3.71**. All analytical data were in full agreement. sf532




**(4*E*,9*R*,10*E*)-methyl 11-bromo-3-((*tert*-butyldimethylsilyl)oxy)-9-methoxy-2,4,10-trimethylundeca-4,10-dienoate (S24):** To a 0 °C cold solution of the alcohol **3.71** (1.50g, 3.92 mmol, 1.0 eq.) in DCM (40 mL) was added 2,6-lutidine (1.68 mL, 15.7 mmol, 4.0 eq.) and the solution was stirred for 10 min. TBSOTf (1.80 mL, 7.84 mmol, 2.0 eq.) was added slowly and the mixture was warmed to r.t. and stirred for 20 min, upon which TLC indicated complete consumption of the starting material. Saturated $NaHCO_3$ (15 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (15 mL) and the unified organic layers were dried over sodium sulfate, filtered and the solvents removed. Flash chromatography ($SiO_2$, pentane/$Et_2O$ 9:1) furnished the product (1.54 g, 3.92 mmol, 82%) as a colorless oil. $R_f$ = 0.40 ($SiO_2$, pentane/$Et_2O$, 9:1). **FTIR** (neat): 2930, 2857, 1790, 1461, 1168, 1063, 836, 669, 626 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.14 (q, *J* = 1.4 Hz, 1H), 5.32 (t, *J* = 7.2 Hz, 1H), 4.06 (d, *J* = 9.9 Hz, 1H), 3.66 (s, 3H), 3.55 – 3.51 (m, 1H), 3.19 (d, *J* = 0.8 Hz, 3H), 2.64 – 2.55 (m, 1H), 2.07 – 1.97 (m, 2H), 1.69 (d, *J* = 1.2 Hz, 3H), 1.66 – 1.58 (m, 1H), 1.52 (d, *J* = 0.8 Hz, 3H), 1.49 – 1.35 (m, 2H), 1.33 – 1.24 (m, 1H), 0.92 – 0.86 (m, 2H), 0.82 (s, 9H), -0.02 (s, 3H), -0.06 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 176.47, 141.85, 141.81, 135.14, 135.12, 129.22, 129.21, 105.03, 105.02, 85.43, 81.84, 56.45, 51.60, 44.89, 33.41, 33.37, 27.42, 25.76, 25.57, 25.53, 18.10, 14.36, 14.02, 14.0, 10.39, -4.50, -4.52, -5.34. . **ESI-HRMS** calc. for $C_{22}H_{41}BrNaO_4Si^+$ $[M+Na]^+$: 499.1850, found 499.1851. sf545



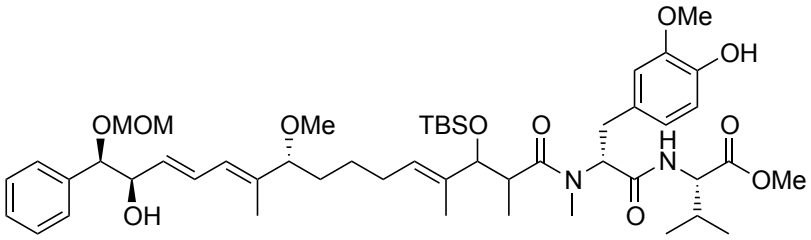
**(9*R*,12*S*)-methyl 5-((*R*,2*E*,8*E*)-9-bromo-7-methoxy-8-methylnona-2,8-dien-2-yl)-12-isopropyl-9-(3-methoxy-4-((triisopropylsilyl)oxy)benzyl)-2,2,3,3,6,8-hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate (3.118):** A biphasic solution of the




methyl ester **S24** (1.54 g, 3.06 mmol, 1.0 eq.) in THF/MeOH/KOH (20 mL, 3:1:1 *v*/*v*/*v*, 10 M KOH in $H_2O$) in a 20 mL microwave vial was heated to 80 °C for 4 h, after which no signal of the methyl ester function was observed in the $^1$H NMR spectrum of an aliquot (TLC is misleading when monitoring this hydrolysis, as a byproduct with the same $R_f$ as the starting material is observed). The solution was acidified to pH 1 with HCl (40 mL, 1 M), upon which a white emulsion formed. The layers were separated, the aqueous phase extracted with $Et_2O$ (3 x 30 mL), dried over sodium sulfate, filtered and the solvents removed. The obtained crude oil appeared to still contain some water (small droplets and turbid oil) and was therefore dissolved in ether (20 mL), dried over sodium sulfate, filtered and the solvents removed *in vacuo* to give the crude acid **3.117** (1.49 g, 3.06 mmol, 99%), which was directly used in the next step without further purification.
The flask containing the crude acid **3.117** (1.49 g, 3.06 mmol, 1.20 eq.) was purged with argon three times and the acid dissolved in dry DCM (5 mL, 0.6 M). DMF (2 drops) was added and the solution was cooled to 0 °C, after which oxalyl chloride (4.36 mL, 50.8 mmol, 20.0 eq.) was added slowly. The mixture was stirred at 0 °C for 10 min and at r.t. for 30 min, after which the solvents and excess reagent were removed *carefully* under high vacuum with an additional cooling trap until a yellow sticky oil remained and bubbling had ceased. This oil was dissolved in dry DCM (5 mL, 0.6 M) and cooled to 0 °C. A suspension of the hydrochloride salt **3.112** (1.42 g, 2.54 mmol, 1.0 eq.), $NEt_3$ (2.86 mL, 20.3 mmol, 8.0 eq.) and DMAP (31 mg, 0.25 mmol, 0.10 eq.) in dry DCM (5 mL) was added to the 0 °C cool solution of the acid chloride and the resulting brown suspension was allowed to warm to r.t. and stirred for 1 h. The mixture was then diluted with $Et_2O$ (50 mL) and washed with aqueous HCl (30 mL, 1 M), water (40 mL) and saturated aqueous $NaHCO_3$ (30 mL), dried over sodium sulfate, filtered and the solvents removed *in vacuo*. The obtained brown crude oil was subjected to flash chromatography ($SiO_2$, pentane/$Et_2O$ 2:3) to furnish the product **3.118** (1.20 g, 2.54 mmol, 50%) as a colorless oil and a mixture of inseparable diastereomers (6:4), as the α-position of the

acid had epimerized. $R_f$ = 0.40 ($SiO_2$, pentane/$Et_2O$, 2:3). **$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 2.0 Hz, 1H), 6.78 – 6.61 (m, 3H), 6.14 (dd, *J* = 5.1, 1.1 Hz, 1H), 5.40 – 5.34 (m, 2H), 4.45 (dd, *J* = 8.2, 5.1 Hz, 1H), 4.14 (d, *J* = 9.5 Hz, 1H), 3.88 – 3.80 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.65 -3.60 (m, 1H), 3.55 – 3.51 (m, 1H), 3.19 (s, 3H), 3.05 (s, 3H), 2.94-2.71 (m, 2H), 2.08 – 1.95 (m, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.56 (s, 1H), 1.49 – 1.38 (m, 2H), 1.07 (d, J = 3.2 Hz, 18H), 0.86 (s, 9H), 0.84 – 0.77 (m, 6H), 0.05 (s, 3H), – 0.03 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 177.25, 171.57, 169.89, 155.76, 144.16, 141.71, 129.50, 129.73, 119.16, 121.57, 120.11, 113.64, 104.83, 85.26, 81.69, 57.14, 57.12, 56.15, 55.40, 51.87, 40.57, 34.84, 33.19, 31.25, 31.0, 27.18, 25.77, 25.66, 25.31, 19.12, 18.86, 18.02, 17.81, 13.78, 12.75, 10.36, -4.56, -5.12. **ESI-HRMS** calc. for $C_{47}H_{83}BrN_2O_8Si_2^+$ $[M+Na]^+$: 939.4944, found 939.4943. sf548

**(5*R*,6*R*,7*E*,9*E*,11*R*,15*E*,21*R*,24*S*)-methyl 17-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-21-(4-hydroxy-3-methoxybenzyl)-24-isopropyl-11-methoxy-10,16,18,20-tetramethyl-19,22-dioxo-5-phenyl-2,4-dioxa-20,23-diazapentacosa-7,9,15-trien-25-oate (3.120):** In a round bottom flask tetrabutylammonium diphenylphosphinate (54 mg, 117 mmol, 4.5 eq.) was dried under high vacuum (heat gun at low setting, ca. 150 °C), whereupon the solid first melted and ceased bubbling after ca. 4 min. The flask was then purged with argon and cooled to r.t.



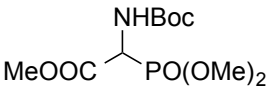

In a separate flask, stannane **3.27** (16 mg, 31 mmol, 1.2 eq.) and vinyl bromide **3.118** (26 mg, 26 mmol, 1.0 eq.) were dissolved in dry DMF (1 mL) and degassed by bubbling argon through the solution for 20 min, after which it was transferred to the flask containing the dried phosphinate. Copper(I) thiophene-2-carboxylate (17 mg, 91 mmol, 3.50 eq.) and $Pd(PPh_3)_4$ (13 mg, 26 mmol, 1.0 eq., yellow crystalline flakes) were added and the mixture turned from bright yellow to dark brown within 10 minutes. After 30 min TLC indicated complete consumption of the stannane, but bromide was still present, and the reaction was therefore sealed with a Teflon fitted glass stopper and stirred overnight at 70 °C. TLC then also indicated complete consumption of the bromide, and the black reaction mixture was diluted with $Et_2O$ (7 mL), washed with water (3 x 3 mL),

dried over sodium sulfate, filtered and dried *in vacuo*. The purple crude oil was purified by flash chromatography ($SiO_2$, $Et_2O$) to give the product **3.120** (15 mg, 26 mmol, 63%) as a yellow oil and a mixture of partially separable diastereomers (6:4). $\boldsymbol{R_f}$ = 0.35 ($SiO_2$, $Et_2O$). **FTIR** (neat): 3355, 2931, 2360, 1743, 1517, 1271, 1207, 1151, 1100, 1034, 912, 837, 701 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.36 – 7.27 (m, 5H), 6.78 – 6.71 (m, 3H), 6.44 (ddd, *J* = 15.3, 11.0, 1.4 Hz, 1H), 5.86 (d, *J* = 11.0 Hz, 1H), 5.63 (s, 1H), 5.45 (dd, *J* = 15.2, 5.6 Hz, 1H), 5.40 – 5.32 (m, 2H), 4.63 – 4.57 (m, 2H), 4.45 (d, *J* = 7.5 Hz, 1H), 4.28 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.24 (d, *J* = 9.4 Hz, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.38 (s, 3H), 3.53-3.39 (m, 2H) 3.12 (s, 3H), 3.07 (s, 3H), 3.04-3.02 (m, 1H), 2.99 – 2.92 (m, 1H), 2.59 (dd, *J* = 12.9, 2.8 Hz, 1H), 2.09 – 1.97 (m, 3H), 1.58 (d, *J* = 0.9 Hz, 3H), 1.56 (s, 3H), 1.53 – 1.34 (m, 4H), 0.87 (d, *J* = 7.5 Hz, 2H), 0.86 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), -0.03 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 177.49, 172.0, 170.59, 144.28, 146.34, 134.85, 133.85, 133.81, 133.59, 131.67, 130.10, 129.24, 128.23, 127.40, 126.57, 114.05, 123.54, 122.20, 112.14, 111.86, 94.28, 86.72, 82.03, 81.85, 75.25, 57.17, 57.16, 57.14, 56.98, 54.01, 49.97, 40.19, 33.37, 33.08, 33.08, 30.75, 29.86, 29.84, 27.11, 25.96, 18.57, 17.93, 13.80, 10.52, 10.52, -4.52, -5.02. **ESI-HRMS** calc. for $C_{50}H_{78}N_2NaO_{11}Si^+$ $[M+Na]^+$: 933.5267, found 933.5259. sf556 sf557

**Methyl (*tert*-butoxycarbonyl)glycinate** (**S25**):[315] To a solution of methyl glycinate MeOOC⌒NHBoc hydrochloride (**3.96**) (10.0 g, 80.0 mmol, 1.0 eq.) in $CHCl_3$ (70 mL) a solution of sodium bicarbonate (6.72 g, 80.0 mmol, 1.0 eq.) in water (120 mL) was added, then a solution of di-*tert*-butyl dicarbonate (17.4 g, 80.0 mmol, 1.0 eq.) in $CHCl_3$ (15 mL) was added and finally sodium chloride (15.0 g) was added. The mixture was stirred at reflux for 2 h before the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 x 60 mL) and the unified organic fractions were dried over $MgSO_4$, filtered, the solvent was removed under reduced pressure and the title compound **S25** (14.6 g, 77.0 mmol, 96%) was obtained as colorless oil. $\boldsymbol{R_f}$ = 0.72 ($SiO_2$, DCM/MeOH, 9:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 5.0 (br. s, 1H), 3.92 (d, *J* = 5.6 Hz, 2H), 3.75 (s, 3H), 1.45 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 170.81, 155.66, 80.04, 52.23, 42.30, 28.31, 27.42.

[315] J. Fischer, H. Ritter, *Beilstein J. Org. Chem.* **2013**, *9*, 2803.

**Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(dimethoxyphosphoryl)acetate (3.97)**:[316]




To a solution of azobisisobutyronitrile (250 mg, 1.52 mmol, 2 mol%) in $CCl_4$ (130 mL), methyl(*tert*-butoxycarbonyl)glycinate (**S25**) (14.4 g, 76.0 mmol, 1.0 eq.) was added and afterwards *N*-bromosuccinimide (14.7 g, 83.0 mmol, 1.09 eq.) was added. The flask was irradiated with a mercury lamp (150 W) and stirred at reflux for 2 h. The suspension was allowed to cool to room temperature and was filtered. The residue was extracted with DCM (20 mL). The filtrate was concentrated under reduced pressure, resulting in a yellow oil of methyl 2-bromo-2-[(*tert*-butoxycarbonyl)amino]acetate **S26** (20.4 g, 76.0 mmol, 100%), which was immediately used in the next step without further purification. $\boldsymbol{R_f}$ = 0.21 ($SiO_2$, DCM/MeOH, 9:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.29 (d, *J* = 9.5 Hz, 1H), 6.18 – 6.01 (m, 1H), 3.78 (s, 3H), 1.40 (s, 9 H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 177.98, 166.56, 152.24, 65.69, 53.44, 28.01.

The following reaction as well as the removal of the trimethyl phosphite on the rotavap should be performed in an extremely well ventilated hood. In a 250 mL round bottom flask equipped with a reflux condenser the bromide **S26** (20.3 g, 76.0 mmol, 1.0 eq.) was dissolved in DCM (150 mL) under vigorous stirring. Trimethyl phosphite (9.43 mL, 80.0 mmol, 1.05 eq.) was added upon which the solution began to reflux and the mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure (very smelly). Subsequent flash chromatography ($SiO_2$, EtOAc/$Et_2O$ 3:1) furnished the phosphonate **3.97** (13.6 g, 45.7 mmol, 60%) as a yellow oil which became solid after being stored at -20 °C overnight. $\boldsymbol{R_f}$ = 0.41 ($SiO_2$, EtOAc/$Et_2O$ 3:1). **FTIR** (neat): 3251, 3061, 2961, 2857, 1757, 1708, 1542, 1436, 1300, 1246, 1157, 1050, 1025, 917, 879, 830 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 5.35 (d, *J* = 9.5 Hz, 1H), 4.86 (ddd, *J* = 21.9, 10.2, 2.8 Hz, 1H), 3.84 – 3.79 (m, 9H), 1.45 – 1.42 (m, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 167.50, 154.89, 80.94, 54.03 (t, *J* = 6.0 Hz ), 53.26, 50.92, 28.18. **$^{31}$P NMR**(162 MHz, $CDCl_3$) δ = 18.87. **ESI–HRMS** calc. for $C_{10}H_{21}NO_7P^+$ $[M+H]^+$: 298.1056, found 298.1050.

[316] T. Nakajima, K. Nakayama, I. Shimizu, *J. Label. Compd. Radiopharm.* **2007**, *50,* 622.

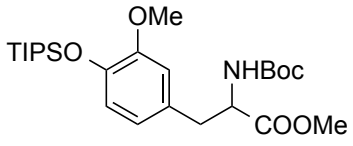
**3-Methoxy-4-[(triisopropylsilyl)oxy]benzaldehyde** (**3.101**):[317] An oven-dried 250 mL two necked round bottom flask equipped with a dropping funnel was charged with imidazole (21.8 g, 320 mmol, 4.0 eq.), 4-hydroxy-3-methoxybenzaldehyde (12.2 g, 80.0 mmol, 1.0 eq.) and DMF (50 mL). At 0 °C neat chlorotriisopropylsilane (17.0 ml, 80.0 mmol, 1.0 eq.) was added drop wise via the dropping funnel to the clear solution, giving a colorless suspension. After stirring for further 10 min at 0 °C, the reaction was allowed to warm to room temperature. TLC indicated full consumption of the starting material after 1 h. The suspension was diluted with $Et_2O$ (200 mL), washed with $H_2O$ (6 x 100 mL), brine (100 mL) and dried over magnesium sulfate. After removal of the solvent the aldehyde **3.101** (23.4 g, 72.4 mmol, 91%) was obtained as a colorless viscous oil. NMR indicated minor impurities of ~4% of TIPSOH. All analytical data were in full agreement with the literature. $\boldsymbol{R_f}$ = 0.82 ($SiO_2$, pentane/$Et_2O$, 9:1). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.84 (s, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 1.34 – 1.20 (m, 3H), 1.10 (d, *J* = 7.4 Hz, 18H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 190.98, 151.83, 151.59, 130.60, 126.21, 120.14, 110.04, 65.85, 55.44, 17.82, 12.94.

**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}acrylate** (**3.98**): To a 0°C cold solution of the phosphonate **3.97** (8.99 g, 30.3 mmol, 1.0 eq.) in DCM (100 mL) was added drop wise DBU (5.07 g, 33.3 mmol, 1.1 eq.), upon which the reaction mixture turned yellow. After further stirring at 0 °C for 15 min, a solution of the aldehyde **3.101** (18.6 g, 60.5 mmol, 2.0 eq.) in DCM (20 mL) was added drop wise. The reaction was allowed to warm to room temperature and stirring was continued for 1 h (Longer reaction time leads to an increase of byproducts). The organic layer was extracted with aqueous citric acid (10%, 2 x 100 ml,) and $H_2O$ (100 mL), dried over sodium sulfate, filtered and the solvents were removed. Flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:2) gave the title compound **3.98** (14.5 g, 21.0 mmol, 69%) as a colorless solid. **M.p.**: 100 – 102 °C. $\boldsymbol{R_f}$ = 0.21 ($SiO_2$, pentane/$Et_2O$, 3:2). **FTIR** (neat): 3220, 3112, 2944, 2667, 1705, 1594, 1507, 1361, 1279, 1165, 1132,

[317] C. Visintin, A. E. Aliev, *Org. Lett.* **2005**, *7*, 1699; R. A. Al-Horani, R. U. Desai, *Tetrahedron* **2012**, *68*, 2027.

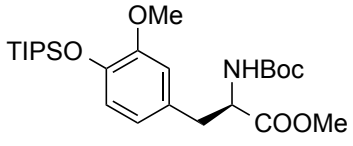
1027, 898, 676 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.25 (s, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.02 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 1.46 – 1.35 (m, 9H), 1.32 – 1.19 (m, 3H), 1.09 (d, *J* = 7.3 Hz, 18H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 166.32, 150.65, 147.05, 131.82, 127.34, 123.80, 120.28, 113.34, 80.78, 55.34, 52.44, 28.16, 17.87, 12.91. **ESI-HRMS** calc. for $C_{25}H_{41}NNaO_6Si^+$ $[M+Na]^+$: 502.2601, found 502.2595.

**Methyl-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(triisopropyl-silyl)oxy]-phenyl}propanoate** (**3.99**): A 20 mL round bottom flask was charged with alkene **3.98**




(176 mg, 0.36 mmol, 1.0 eq.) and Pd/C (18 mg, 0.16 mmol, 0.44 eq., 10% Pd) and then purged three times with argon. MeOH (3 mL) was added and stirring was started. A balloon with $H_2$ (2 L) was attached and after bubbling $H_2$ through the suspension for 10 min, the reaction was stirred overnight under hydrogen atmosphere. After 16 h TLC indicated complete consumption of the starting material and the mixture was filtered repeatedly through a pad of diatomaceous earth until no more grey dust was observed in the filtrate. The solvent was removed under reduced pressure and the title compound **3.99** was obtained as a colorless powder (70.1 mg, 0.14 mmol, 40%). **M.p.** 101 – 104°C. $\boldsymbol{R_f}$ = 0.20 ($SiO_2$, pentane/$Et_2O$, 3:2). **FTIR** (neat): = 3373, 2941, 2866, 1740, 1704, 1506, 1368, 1292, 1223, 1169, 1150, 906, 881 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.78 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.54 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.94 (d, *J* = 8.3 Hz, 1H), 4.53 (q, *J* = 6.7 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.01 – 2.98 (m, 2H), 1.42 (s, 9 H), 1.27 – 1.20 (m, 3 H), 1.07 (d, *J* = 7.5 Hz, 18H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 172.51, 155.07, 150.79, 144.54, 128.96, 121.34, 120.38, 113.04, 79.85, 55.40, 54.54, 52.12, 38.06, 28.32, 17.89, 12.84. **ESI-HRMS** calc. for $C_{25}H_{43}NNaO_6Si^+$: 504.2741, found 504.2752.

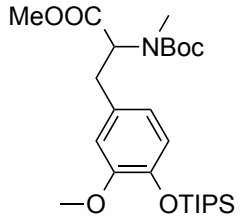
**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl} propanoate** (**3.100**): To a solution of the alkene **3.98** (1.50 g, 3.13 mmol,




1.0 eq.) in EtOAc (10 mL, degassed by bubbling argon for 20 min) in a flame-dried vial was added the catalyst 1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)-rhodium(I) trifluoromethanesulfonate (11.5 mg, 0.01 mmol, 0.50 mol%) and the vial was put into a hydrogenation autoclave. The autoclave was set under

$H_2$ atmosphere (7.5 bar) and stirred for 3 d at room temperature. The reaction mixture was filtered through a pad of silica and extracted with a pentane/ether mixture (1:1, 50 mL) before the solvent was removed at reduced pressure. The title compound **3.100** was obtained as a colorless powder (1.48 g, 3.07 mmol, 98%). $[\alpha]_D$ = –8.3 (*c* = 0.38 acetone). **e.r.** = 98:2 (determined with chiral HPLC; Chiralpak $I_A$, 95:5 heptane/isopropanol, 0.5 mL/min, injection vol.: 1 µL, 25°C, $t_R$ (*R*): 14.5 min, $t_R$ (*S*): 19.5 min.). $R_f$ = 0.20 ($SiO_2$, pentane/$Et_2O$, 3:2). **FTIR** (neat): 3373, 2941, 2866, 1740, 1704, 1506, 1368, 1292, 1223, 1169, 1150, 906, 881 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.78 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.54 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.94 (d, *J* = 8.3 Hz, 1H), 4.53 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 2.99 (d, *J* = 6.1 Hz, 2H), 1.42 (s, 10H), 1.24 – 1.19 (m, 3H), 1.08 (d, *J* = 7.3 Hz, 18H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 172.51, 155.07, 150.79, 144.54, 128.96, 121.34, 120.38, 113.04, 79.85, 55.40, 54.54, 52.12, 38.06, 28.32, 17.89, 12.84. **ESI-HRMS** calc. for $C_{25}H_{43}NNaO_6Si^+$ $[M+Na]^+$: 504.2741, found 504.2748.

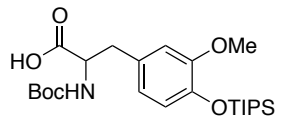
**Methyl-{[*tert*-butoxycarbonyl](methyl)amino}-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}propanoate** (**3.105**): To a 0 °C cold solution of the carbamate **3.100** (1.33



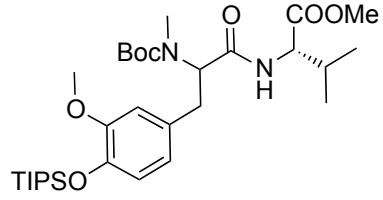

g, 2.78 mmol, 1.0 eq.) in dry DMF (20 mL) was added NaH (167 mg, 4.16 mmol, 1.5 eq., 60% dispersion in mineral oil), after which the mixture turned bright yellow. After stirring for 10 min at 0 °C, methyl iodide was added (1.59 g, 11.1 mmol, 4.0 eq.). The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h (when the reaction is run for longer than 2 h increased byproduct formation is observed by TLC). The reaction was quenched by careful addition of saturated aqueous $NH_4Cl$ (20 mL) and the mixture was extracted with $Et_2O$ (3 x 30 mL). The combined organic layers were washed with $H_2O$ (4 x 70 mL) and dried over sodium sulfate before the solvents were removed. The residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:2) to furnish the methylated carbamate **3.105** (1.28 g, 2.60 mmol, 93%) as a yellowish oil. Racemization occurs under these basic condition as chiral HPLC indicates. Rotamers are visible in the NMR (ca. 2:3, $CDCl_3$). $R_f$ = 0.32 ($SiO_2$, pentane/$Et_2O$, 3:1). $[\alpha]_D$ = +1.2 (*c* = 0.89 acetone). **e.r.**: 46:54 (determined with chiral HPLC; Chiralpak $I_A$, 95:5 heptane/isopropanol, 1 mL/min, injection vol.: 1 µL, 25 °C, $t_R$ (*minor*): 4.12 min, $t_R$

(*major*): 4.43 min). **FTIR** (neat): 2944, 2867, 2010, 1745, 1696, 1584, 1515, 1464, 1392, 1366, 1313, 1280, 1233, 1158, 1074, 1039, 997, 917, 884, 814, 771, 679 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.78 (d, *J* = 7.9 Hz, 1H), 6.72-6.54 (m, 2H), 4.85 (d, *J* = 5.1 Hz, 0.5H), 4.31 (d, *J* = 6.4 Hz, 0.5H), 3.77 (s, 3H), 3.72 (d, *J* = 3.8 Hz, 3H), 3.21 (s, 1H), 2.97 (s, 1H), 2.67 (s, 3H), 1.39 (s, 9H), 1.29-1.18 (m, 3H), 1.07 (d, *J* = 7.2 Hz, 18H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ =172.12, 155.02, 150.76, 144.19, 130.86, 121.07, 120.36, 113.02, 112.71, 62.46, 59.51, 55.41, 52.05, 33.6, 28.24, 17.85, 12.77. **ESI-HRMS** calc. for $C_{26}H_{45}NNaO_6Si^+$ $[M+Na]^+$: 518.2914, found: 518.2908.

**2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}propanoic acid** (**3.106**): To a solution of the ester **3.105** (300 mg, 600 μmol, 1.0 eq.) in a mixture of THF/MeOH/$H_2O$ (3 mL:1 mL:0.4 mL) at 0 °C was slowly added aqueous NaOH (0.6 mL, 1.20 mmol, 2.0 eq.). The mixture was allowed to warm to r.t. and stirred for 1 h before acidification with aqueous citric acid (10%, 10 mL) to pH ~3. Longer reaction times lead to increased cleavage of the TIPS protecting group. The suspension was extracted with $Et_2O$ (4 x 20 mL) and the combined organic layers were dried over sodium sulfate. The solvents were removed and the crude product was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$/acetic acid, 4:1:0.05) to furnish the free acid **3.106** (212 mg, 0.44 mmol, 73%) as a colorless oil. $\boldsymbol{R_f}$ = 0.25 ($SiO_2$, pentane/$Et_2O$/acetic acid, 4:1:0.05). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.79 (d, *J* = 8.0 Hz, 1H), 6.64 (t, *J* = 10.8 Hz, 2H), 4.65 (s, 0.5H), 4.36 (d, *J* = 6.6 Hz, 0.5H), 3.78 (s, 3H), 3.33 – 2.93 (m, 2H), 2.66 (d, *J* = 12.6 Hz, 3H), 1.41 (s, 9H), 1.31 – 1.14 (m, 3H), 1.07 (d, *J* = 6.6 Hz, 18H). **$^{13}$C NMR** (101 MHz, MeOD) δ = 173.81, 155.74, 150.69, 143.93, 131.48, 120.85, 112.798, 63.26, 60.88, 55.64, 35.55, 32.60, 28.37, 21.22, 18.17, 13.87. **ESI-HRMS** calc. for $C_{25}H_{43}NNaO_6Si^+$ $[M+Na]^+$: 504.2758, found: 504.2752.

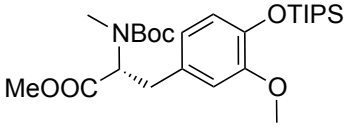



**Methyl {2-[(*tert*-butoxycarbonyl)methyl]amino-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}propanoyl}-*S*-valinate** (**3.107**): To a solution of the acid **3.106** (248 mg, 512 mmol, 1.0 eq.) in dry DCM (2 mL) at 0 °C was added *S*-valine methyl ester hydrochloride (88 mg, 0.52 mmol, 1.02 eq.), HOBt (76.5 mg, 0.56 mmol, 1.20 eq.),



HBTU (215 mg, 0.56 mmol, 1.20 eq.) and diisopropylethylamine (145 mg, 1.13 mmol, 2.20 eq.). The mixture was stirred at r.t. and monitored by UPLC-MS. After 14 h the solution was diluted with EtOAc (5 mL), washed with aqueous HCl (10 mL, 1 M), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) before drying over sodium sulfate, filtration and subsequent removal of the solvent. The residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:2) to furnish the dipeptide **3.107** as a colorless solid (247 mg, 413 mmol, 81%). $\boldsymbol{R_f}$ = 0.31 ($SiO_2$, pentane/$Et_2O$, 3:2). $\boldsymbol{[\alpha]_D}$ = +6.3 (*c* = 0.89 acetone). **FTIR** (neat): 3342, 2944, 2867, 2582, 1744, 1687, 1584, 1513, 1465, 1390, 1283, 1235, 1155, 1038, 998, 903, 813, 684, 632 $cm^{-1}$. **$^1$H NMR** (400 MHz, MeOD) δ = δ 7.90 – 7.71 (m, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 6.80 – 6.63 (m, 2H), 4.92 – 4.90 (m, 1 H) 4.34 – 4.32 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.26 – 3.10 (m, 1H), 3.02 – 2.84 (m, 1H), 2.25 – 2.05 (m, 1H), 1.42 (d, *J* = 2.4 Hz, 9H), 1.36 – 1.18 (m, 3H), 1.12 (d, *J* = 6.6 Hz, 18H), 0.94 (m, 6H). **$^{13}$C NMR** (101 MHz, MeOD) δ = 171.97, 156.61, 150.65, 143.94, 130.53, 120.85, 119.87, 112.65, 80.05, 61.08, 57.71, 54.41, 51.10, 34.03, 30.34, 27.18, 16.96, 12.65. **ESI-HRMS** calc. for $C_{31}H_{54}N_2NaO_7Si^+$ $[M+Na]^+$: 617.3598, found: 617.3592.

**(*R*)-methyl-((*tert*-butoxycarbonyl)(methyl)amino)-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}propanoate** (**3.111**): Silver(I) oxide was prepared from silver nitrate.[318] A solution of NaOH (3.8 mL, 71 mmol, 1.1 eq., 50% w/w in water) was added slowly to a boiling solution of $AgNO_3$ (11 g, 65 mmol, 1.0 eq.) in water (500 mL). A brown solid formed immediately. The precipitate was filtered, extracted with water, acetone, $Et_2O$ and dried *in vacuo* to give a dark brown amorphous solid (7.1 g, 30 mmol, 93%). The compound was preferably used within the next 2 days. The methylation reaction does not reach complete conversion if old $Ag_2O$ is used.

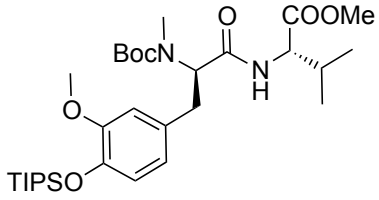



To a solution of methyl carbamate **3.100** (1.55 g, 3.06 mmol, 1.0 eq.) in DMF (16 mL) was added *freshly prepared* (!) $Ag_2O$ (7.1 g, 30 mmol, 10 eq.) and methyl iodide (9.62 mL g, 150 mmol, 50 eq.). The flask was wrapped in aluminum foil to exclude light, sealed with a glass stopper with a metal clamp and stirred at 40 °C overnight, after which a grey-white precipitate had formed. The brown-grey suspension was filtered

[318] P. Danner, M. Morkunas, M. E. Maier, *Org. Lett.* **2013**, *15*, 2474.

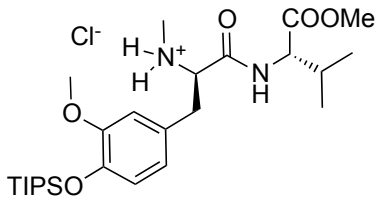
though a frit and washed with $Et_2O$ (120 mL), washed with water (5 x 25 mL) and dried over sodium sulfate. Removal of the solvents gave the methylated amine **3.111** (1.47 g, 2.97 mmol, 97%) as a yellowish oil. All analytical data were in full agreement with the racemic compound **3.110**. **[a]$_D$**= +44.6 (*c* = 0.39 $CHCl_3$). **e.r.**: 99:1 (determined with chiral HPLC; Chiralpak $I_A$, 95:5 heptane/isopropanol, 1 mL/min, injection vol.: 1 μL, 25 °C, $t_R$ (*S*): 4.12 $t_R$ (*R*): 4.43. sf496

**(*S*)-methyl 2-((*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)propanamido)-3-methylbutanoate (S28):** The




compound was prepared in analogy to the procedure described for the racemate **3.107**. Enantiomerically pure amino ester **3.111** (2.20 g, 4.22 mmol) gave in two steps (without chromatography of the intermediate crude acid) the title compound **S28** (2.07 g, 3.30 mmol, 78% over two steps) as a pure diastereoisomer with a ratio of rotamers of about 2:1. All analytical data were in full agreement with the diastereomeric mixture, except optical rotation, $^1$H NMR and $^{13}$C NMR. **[α]$_D$** = +59.3 (*c* = 0.75 $CHCl_3$). NMR data is given for the major rotamer: **$^1$H NMR** (400 MHz, $CDCl_3$) δ = δ 6.83 – 6.56 (m, 3H), 4.94 – 4.86 (m, 1H), 4.45 (dd, *J* = 8.7, 4.6 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.25 (dd, *J* = 14.5, 6.9 Hz, 1H), 2.89 (dd, *J* = 14.5, 9.3 Hz, 1H), 2.71 (s, 3H), 2.19 – 2.11 (m, 1H), 1.42 (s, 9H), 1.28 – 1.16 (m, 1H), 1.06 (d, J = 7.4 Hz, 18H), 0.93 – 0.87 (m, 3H), 0.87 – 0.81 (m, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 172.12, 170.95, 159.79, 150.64, 143.89, 130.43, 120.98, 120.12, 112.50, 80.41, 59.35, 56.92, 55.22, 51.86, 33.11, 30.82, 30.67, 18.83, 17.68, 17.31, 12.61. sf498

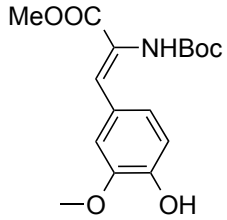
**(*R*)-1-(((*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-*N*-methyl-1-oxopropan-2-aminium chloride (3.112):**



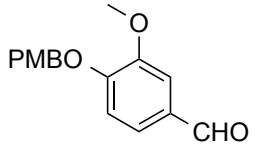

The Boc-protected dipeptide **S28** (1.26 g, 2.01 mmol, 1.0 eq.) was dissolved in HCl (6 mL, 4 M in dioxane, 0.3 M) and stirred at r.t. until TLC indicated complete consumption of the starting material (usually ca. 30 min). The solvents were removed *carefully* and the crude beige solid was dried under high vacuum to give the hydrochloride salt **3.112** (1.05 g, 2.01 mmol, 98%) as a beige amorphous solid. All analytical data were in full agreement with the diastereomeric

mixture, except optical rotation, $^{1}$H NMR and $^{13}$C NMR. $R_f$ = 0.00 ($SiO_2$, pentane/$Et_2O$, 3:2). $[\alpha]_D$ = –36.3° (*c* = 0.95 $CHCl_3$). **$^{1}$H NMR** (400 MHz, MeOD) δ = 6.73 – 6.70 (m, 2H), 6.60 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.11 (d, *J* = 5.4 Hz, 1H), 4.01 (dd, *J* = 9.7, 5.6 Hz, 1H), 3.70 (s, 3H), 3.62 (s, 2H), 3.02 (dd, *J* = 13.3, 5.5 Hz, 1H), 2.94 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.58 (s, 3H), 1.98 – 1.90 (m, 1H), 1.19 – 1.10 (m, 3H), 0.99 (d, *J* = 7.3 Hz, 18H), 0.67 (d, *J* = 6.9 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3H). **$^{13}$C NMR** (101 MHz, MeOD) δ = 172.72, 168.68, 152.04, 146.10, 127.88, 122.70, 121.49, 114.38, 64.04, 59.69, 55.83, 52.57, 37.46, 32.40, 30.97, 19.33, 18.34, 18.30, 14.07.

**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-hydroxy-3-methoxyphenyl)-acrylate** (**S29**): To a solution of the TIPS protected phenol **3.98** (1.0 g, 2.08 mmol, 1.0 eq.) in dry THF (10 mL) was added TBAF solution (1 M in THF, 2.3 mL, 2.3 mmol, 1.1 eq.) at -40 °C. The solution turned bright yellow and was stirred at -40 °C for 10 min. Then the mixture was allowed to warm to room temperature and stirring was continued for 1 h. The reaction was quenched with saturated aqueous $NH_4Cl$ solution (10 mL), then extracted with $Et_2O$ (4 x 30 mL), dried over sodium sulfate and the solvent was removed at reduced pressure. The residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 3:1) to furnish the deprotected phenol **S29** (618 mg, 1.91 mmol, 92%) as a colorless oil. $R_f$ = 0.27 ($SiO_2$, pentane/$Et_2O$, 3:1). **FTIR** (neat): 3763, 3404, 3209, 3163, 3086, 2983, 2926, 1690, 1598, 1513, 1430, 1357, 1303, 1251, 1211, 1154, 1028, 994, 953, 908 cm$^{-1}$. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 7.10 (s, 1H), 7.04 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.01 (s, 1H), 5.74 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 1.35 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 166.32, 146.99, 146.29, 131.73, 126.41, 124.68, 114.45, 111.86, 80.85, 69.82, 55.82, 52.50, 28.17. **ESI-HRMS** calc. for $C_{16}H_{21}NNaO_6^+$ $[M+Na]^+$: 346.1267, found: 346.1261.



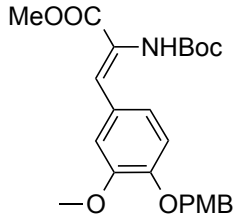

**3-Methoxy-4-[(4-methoxybenzyl)oxy]benzaldehyde** (**S30**):[319] To a suspension of vanillin (1.00 g, 6.51 mmol, 1.0 eq.), tetrabutylammonium iodide (481 mg, 1.30 mmol, 0.20 eq.) and $K_2CO_3$ (1.08 g, 7.81 mmol,




[319] P. Ploypradith, P. Cheryklin, N. Niyomtham, D. R. Bertoni, S. Ruchirawat, *Org. Lett.* **2007**, *9*, 2637.

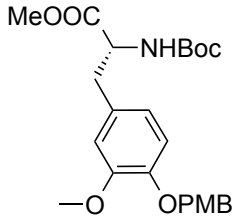
1.20 eq.) in dry acetone (30 mL) was added 4-methoxybenzyl chloride (1.22 g, 7.81 mmol, 1.20 eq.) and the resulting mixture was stirred at reflux for 18 h. TLC indicated full consumption of starting material and water (30 mL) and DCM (20 mL) were added and the layers separated. The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (80 mL) and dried over sodium sulfate. The solvents were removed and the crude oil was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 2:3) to give the PMB protected phenol **S30** (830 mg, 3.05 mmol, 47%) as a yellowish solid. All analytical data were in full agreement with the literature. $\boldsymbol{R_f}$ = 0.27 ($SiO_2$, pentane/$Et_2O$, 2:3). **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.84 (s, 1H), 7.46 – 7.33 (m, 4H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.95 – 6.87 (m, 2H), 5.17 (s, 2H), 3.93 (s, 3H), 3.81 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 191.07, 159.78, 153.86, 150.25, 130.36, 129.18, 128.15, 126.76, 114.28, 112.56, 109.47, 70.87, 56.19, 55.45.

**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(4-methoxybenzyl)-oxy]phenyl}acrylate** (**S31**): To a solution 0 °C cold solution of the phosphonate **3.97**



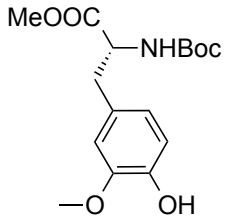

(293 mg, 1.0 mmol, 1.0 eq.) in DCM (3 mL) was added drop wise DBU (183 mg, 1.20 mmol, 1.20 eq.), upon which the reaction mixture turned yellow. After stirring at 0 °C for 15 min, the aldehyde **S30** (327 mg, 1.20 mmol, 1.20 eq.) was added in small portions and the reaction was allowed to warm to room temperature and stirring was continued for 1 h (longer reaction time leads to an increase of byproducts). The organic layer was extracted with aqueous citric acid (10%, 10 mL), $H_2O$ (10 mL), dried over sodium sulfate and the solvents removed. Flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:2) gave the title compound **S31** as a colorless solid (200 mg, 450 mmol, 46%). $\boldsymbol{R_f}$ = 0.27 ($SiO_2$, pentane/$Et_2O$, 3:1). **FTIR** (neat): 3227, 3110, 2976, 2874, 1720, 1696, 1595, 1514, 1462, 1435, 1355, 1246, 1151, 1030, 992, 811, 779, 726, 654 cm$^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ= 7.35 (d, *J* = 8.6 Hz, 2H), 7.25 (s, 1H), 7.20 (d, *J* = 1.6 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.88 (t, *J* = 8.6 Hz, 3H), 5.11 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 1.40 (s, 9H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 166.40, 159.60, 149.48, 129.13, 128.84, 127.30, 114.16, 113.48, 112.95, 70.75, 56.0, 55.43, 52.64, 28.30. **ESI-HRMS** calc. for $C_{24}H_{29}NNaO_7^+$ $[M+Na]^+$: 466.1842, found: 466.1836.

**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(4-methoxy-benzyl)-oxy]phenyl}propanoate** (**S32**): A flame-dried 5 mL vial with a screw cap was charged




with the alkene **S31** (80.0 mg, 0.18 mmol, 1.0 eq.) and the catalyst 1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano]benzene-(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (1.33 mg, 1.80 μmol, 1 mol%) was added. The two solids were dissolved in a DCM/EtOAc mixture (1.5 mL, 1:2 *v*/*v*, degassed by argon bubbling for 20 min) and the open vial put into a hydrogenation autoclave. The reaction was set under $H_2$ atmosphere (7.5 bar) and stirred for 5 d at RT. The mixture was then diluted with pentane (2 mL) and filtered through a short pad of silica. After rinsing the pad with $Et_2O$ (20 mL) the solvents were removed under reduced pressure to obtain the title compound **S32** (79.0 mg, 0.17 mmol, 98%) as a yellowish solid. $\boldsymbol{R_f}$ = 0.27 ($SiO_2$, pentane/$Et_2O$, 3:1). $\boldsymbol{[a]_D}$= –35.2 (*c* = 0.93 $CHCl_3$). **FTIR** (neat): 3362, 2939, 2875, 2840, 2361, 2118, 1740, 1690, 1613, 1588, 1513, 1451, 1367, 1294, 1249, 1226, 1160, 1027, 998, 867, 802, 752, 618 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 2H), 6.68 – 6.56 (m, 2H), 5.03 (d, *J* = 11.0 Hz, 2H), 4.95 (d, *J* = 7.1 Hz, 1H), 4.55 (dd, *J* = 12.8, 5.0 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 3.07 – 2.96 (m, 2H), 1.42 (s, 9H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 129.07, 129.05, 121.39, 114.11, 113.96, 112.89, 77.21, 70.84, 55.88, 55.26, 52.17, 37.90, 28.26. **ESI-HRMS** calc. for $C_{24}H_{31}NNaO_7^+$[M+Na]$^+$: 468.1999, found: 468.1993.

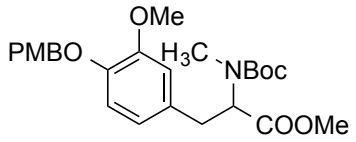
**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-hydroxy-3-methoxyphenyl)-propanoate** (**S33**): A suspension of hydrogenation product **S32** (20.0 mg, 44.9 mmol,




1.0 eq.) and Pd/C (10%, 4.78 mg, 4.49 mmol, 0.1 eq.) in MeOH (2 mL) was purged with $H_2$ for 5 min and then stirred under a hydrogen atmosphere overnight. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 2:3) to furnish the phenol **S33** as a colorless oil (10.0 mg, 30.7 mmol, 68%). $\boldsymbol{R_f}$ = 0.32 ($SiO_2$, pentane/$Et_2O$, 2:3). $\boldsymbol{[\alpha]_D}$ = –34.0 (*c* = 0.5 $CHCl_3$). **e.r.** = 97:3 determined with chiral HPLC; Chiralpak $I_A$, 80:20 hexane/isopropanol, 1.0 mL/min, injection vol.: 5 μL, 25 °C, $t_R$ (*R*): 7.4 min, $t_R$ (*S*): 10.6 min. **FTIR** (neat): 3370, 3336, 3009, 2979, 2933, 2359, 2117, 2053, 1737, 1687, 1603,

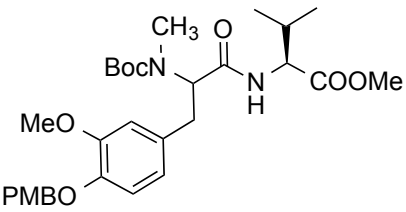
1531, 1441, 1393, 1362, 1271, 1224, 1158, 1065, 1028, 980, 895, 862, 816, 775, 712 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 6.82 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 2H), 5.55 (s, 1H), 4.97 (d, *J* = 7.4 Hz, 1H), 4.54 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.08 – 2.94 (m, 2H), 1.42 (s, 9H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.59, 155.23, 146.61, 144.84, 127.87, 122.23, 114.52, 111.77, 80.07, 55.99, 54.70, 52.33, 38.14, 28.45. **ESI-HRMS** calc. for $C_{16}H_{23}NNaO_6^+$ $[M+Na]^+$: 348.1423, found: 348.1418.

**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(4-methoxybenzyl)oxy]phenyl}propanoate** (**S34**): To a solution of the carbamate **S33**



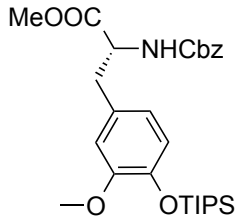

(1.14 g, 2.56 mmol, 1.0 eq.) in dry DMF (40 mL) was added NaH (154 mg, 3.84 mmol, 1.50 eq., 60% suspension in mineral oil) at 0 °C. After stirring for 10 min, MeI (1.45 g, 10.2 mmol, 4.0 eq.) was added and the solution allowed to warm to r.t. After 4 h the reaction mixture was carefully quenched with saturated aqueous $NH_4Cl$ solution (50 mL) and extracted with ether (3 x 30 mL). The combined organic layers were washed with water (4 x 50 mL) and dried over sodium sulfate. After removal of the solvent at reduced pressure the residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 2:3) to furnish the methylated carbamate **S34** as a yellowish oil (1.0 g, 2.19 mmol, 85%). Rotamers are visible in the $^1$H NMR (ca. 2:3, $CDCl_3$). $\boldsymbol{R_f}$ = 0.27 ($SiO_2$, pentane/$Et_2O$, 3:1). **$[a]_D$**= +13.0 (c = 0.85 $CHCl_3$). **FTIR** (neat): 2952, 2361, 1742, 1692, 1612, 1513, 1455, 1391, 1321, 1249, 1139, 1032, 992, 822, 650 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.38 – 7.31 (m, 2H), 6.93 – 6.85 (m, 2H), 6.83 – 6.58 (m, 3H), 5.04 (s, 2H), 4.91 (dd, *J* = 10.8, 5.2 Hz, 0.5H), 4.43 (dd, *J* = 10.5, 4.1 Hz, 0.5H), 3.85 (s, 3H), 3.80 (s, 3H), 3.73 (d, *J* = 7.6 Hz, 3H), 3.32 – 3.10 (m, 1H), 3.01 – 2.90 (m, 1H), 2.70 (d, *J* = 6.5 Hz, 2H), 1.44 – 1.28 (m, 9H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ =165.59, 155.94, 153.18, 135.23, 129.03, 121.0, 113.94, 112.67, 86.15, 70.90, 67.94, 61.97, 59.34 55.76, 55.27, 52.12, 34.75, 32.40, 28.20. **ESI-HRMS** calc. for $C_{25}H_{33}NNaO_7^+$ $[M+Na]^+$: 482.2155, found: 482.2149.

**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(4-methoxybenzyl)oxy]phenyl}propanoyl-*S*-valinate** (**S35**): The methyl ester **S34** (452 mg, 980 mmol, 1.0 eq.) was dissolved in a mixture of THF/MeOH/$H_2O$ (6:2:1 *v*/*v*/*v*, 14 mL). A solution of NaOH (1.48 mL, 2.95 mmol, 3.0 eq., 2M in water) was then added and the solution was stirred for 30 min at r.t. The reaction mixture was extracted with diethylether (3 x 30 mL) to remove byproducts and the aqueous phase was then acidified with 1 M HCl to pH ~2, where the formation of a white precipitate could be observed. The suspension was extracted with $Et_2O$ (3 x 40 mL) and the combined organic phases were dried over sodium sulfate before removal of the solvent. The crude oil was used directly in the next step without further purification**.**



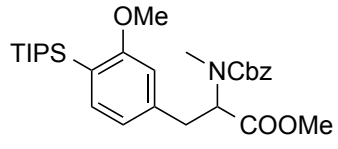

The crude acid was dissolved in DCM (4 mL) and cooled to 0 °C. *S*-valine methyl ester hydrochloride (157 mg, 0.94 mmol, 1.02 eq.), HOBt (137 mg, 1.01 mmol, 1.20 eq.), HBTU (384 mg, 1.01 mmol, 1.20 eq.) and diisopropylethylamine (262 mg, 2.02 mmol, 2.20 eq.) were added. The suspension was allowed to warm to r.t. and stirred for 14 h. The reaction mixture was then diluted with EtOAc (5 mL), washed with aqueous HCl (10 mL, 1 M), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). After drying over sodium sulfate, filtration and subsequent removal of the solvent at reduced pressure the residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 2:3) to furnish the dipeptide **S35** (382 mg, 682 μmol, 70% over 2 steps) as a colorless oil. $\boldsymbol{R_f}$ = 0.31 ($SiO_2$, pentane/$Et_2O$, 3:2). $\boldsymbol{[\alpha]_D}$ = +21.5 (*c* = 0.5 $CHCl_3$). **FTIR** (neat): 3353, 2965, 2876, 2838, 2336, 2049, 1741, 1683, 1612, 1588, 1512, 1463, 1398, 1320, 1249, 1141, 1033, 957, 865, 822, 770, 737, 653, 623 $cm^{-1}$. **$^1$H NMR** (400 MHz, MeOD) δ = 7.33 (d, *J* = 8.6 Hz, 2H), 6.98 – 6.82 (m, 4H), 6.73 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.98 (s, 2H), 4.32 (d, *J* = 6.2 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H), 2.79 (s, 3H), 2.13 (s, 1H), 1.38 (s, 9H), 0.89 (s, 6H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ =172.0, 159.60, 149.79, 130.50, 129.31, 121.02, 114.81, 112.85, 72.19, 60.61, 59.17, 56.41, 55.64, 52.47, 35.43, 35.43, 35.39, 31.49, 31.68, 28.54, 28.49, 19.12, 18.98. **ESI-HRMS** calc. for $C_{30}H_{42}N_2NaO_8^+$ $[M+Na]^+$: 581.2839, found: 581.2833.

**Methyl (*R*)-2-{[(benzyloxy)carbonyl]amino}-3-{3-methoxy-4-[(triisopropyl-silyl)-oxy]phenyl}propanoate** (**3.109**): To a 0 °C cold solution of the carbamate **3.100** (502 mg, 1.04 mmol, 1.0 eq.) in dry DCM (2 mL) TFA (2 mL) was added slowly. After 30 min, TLC indicated full consumption of the starting material and the solvents were removed under reduced pressure. After carefully drying under high vacuum, the residue was directly used in the next step.



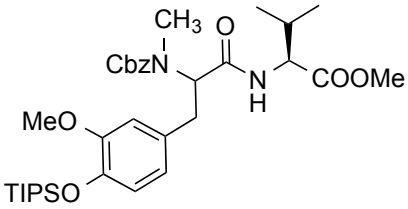

The crude product was dissolved in a mixture of $Et_2O$ (4.5 mL) and $H_2O$ (6 mL) and $Na_2CO_3$ was added (276 mg, 2.60 mmol, 2.50 eq.). After stirring for 10 min, benzyl chloroformate (177 mg, 1.04 mmol, 1.0 eq.) was added drop wise. The mixture was then stirred at room temperature for 14 h. The suspension was diluted with $Et_2O$ (5 mL) and the organic phase was washed with brine (2 x 20 mL) and dried over sodium sulfate. After removal of the solvent at reduced pressure, the residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:1) to obtain the Cbz-protected compound **3.109** (512 mg, 0.99 mmol, 96% over 2 steps) as a colorless oil. $\boldsymbol{R_f}$ = 0.37 ($SiO_2$, pentane/$Et_2O$ 3:1). $\boldsymbol{[\alpha]_D}$ = –33.8 (*c* = 0.67 $CHCl_3$). **FTIR** (neat): 3339, 3034, 2945, 2866, 1722, 1585, 1512, 1462, 1346, 1280, 1236, 1211, 1160, 1128, 1038, 883, 818, 774, 738, 679 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.41 – 7.28 (m, 5H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.65 – 6.43 (m, 2H), 5.19 (d, *J* = 8.1 Hz, 1H), 5.09 (q, *J* = 12.3 Hz, 2H), 4.71 – 4.50 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.08 – 2.96 (m, 2H), 1.31 – 1.16 (m, 3H), 1.07 (d, *J* = 7.2 Hz, 18H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.23, 155.72, 150.99, 144.77, 136.39, 128.88, 128.76, 128.67, 128.54, 128.33, 128.24, 121.49, 120.57, 113.11, 67.07, 55.51, 55.07, 52.37, 38.16, 18.01, 12.95. **ESI-HRMS** calc. for $C_{28}H_{41}NNaO_6Si^+$ $[M+Na]^+$: 538.2601, found: 538.2595.

**Methyl (*R*)-2-{[(benzyloxy)carbonyl](methyl)amino}-3-{3-methoxy-4-[(triisopropyl-silyl)oxy]phenyl}propanoate** (**S36**): To a solution of the carbamate **3.109** (539 mg, 1.05 mmol, 1.0 eq.) in dry DMF (8 mL) was added NaH (50.0 mg, 1.25 mmol, 1.20 eq., 60% dispersion in mineral oil) at 0 °C. After stirring for 20 min, MeI (593 mg, 4.18 mmol, 4.0 eq.) was added and the reaction mixture was allowed to warm to r.t. After 1.5 h, the reaction was carefully quenched with saturated aqueous $NH_4Cl$ (20 mL) and then



extracted with $Et_2O$ (3 x 30 mL). The combined organic layers were then washed with water (3 x 80 mL) and dried over sodium sulfate. After removal of the solvent, the crude product was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:2) to furnish the methylated carbamate **S36** (463 mg, 0.87 mmol, 83%) as a slightly yellow oil. $\boldsymbol{R_f}$ = 0.31 ($SiO_2$, pentane/$Et_2O$, 3:2). $\boldsymbol{[\alpha]_D}$ = +9.2 (*c* = 0.42 $CHCl_3$). **FTIR** (neat): 2944, 2866, 2356, 1744, 1703, 1585, 1514, 1460, 1401, 1280, 1234, 1138, 1039, 1005, 884, 618, 767, 734, 677 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.41 – 7.20 (m, 5H), 6.79 – 6.52 (m, 3H), 5.18 – 5.0 (m, 2H), 4.98 – 4.61 (m, 1H), 3.71 (d, *J* = 8.2 Hz, 3H), 3.66 (d, *J* = 4.8 Hz, 3H), 3.33 – 3.12 (m, 1H), 3.08 – 2.86 (m, 1H), 2.79 (d, *J* = 15.5 Hz, 3H), 1.33 – 1.16 (m, 3H), 1.07 (d, *J* = 7.2 Hz, 18H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.78, 156.62, 156.38, 150.97, 144.29, 130.23, 128.59, 128.15, 128.04, 127.72, 121.09, 120.53, 112.85, 112.68, 109.75, 67.54, 67.34, 61.37, 60.48, 55.51, 52.37, 35.14, 34.71, 32.78, 31.99, 18.02, 17.84, 12.95. **ESI-HRMS** calc. for $C_{29}H_{43}NNaO_6Si^+$ $[M+Na]^+$: 552.2758, found: 552.2752.

**Methyl [(*R*)-2-{[(benzyloxy)carbonyl](methyl)amino}-3-{3-methoxy-4-[(triiso-propylsilyl)oxy]phenyl}propanoyl]-*S*-valinate** (**S37**): To a solution of the methyl ester




**S36** (423 mg, 793 μmol, 1.0 eq.) in THF/MeOH/$H_2O$ (6:2:1 *v*/*v*/*v*, 9 mL) was added aqueous NaOH (0.59 mL, 1.20 mmol, 1.50 eq., 2 M) and the mixture was stirred for 30 min. The reaction mixture was then acidified with 1 M HCl to pH ~2, where the formation of a white precipitate could be observed. The suspension was extracted with $Et_2O$ (3 x 40 mL) and the combined organic layers were dried over sodium sulfate before removal of the solvent. The crude acid was directly used in the next step.

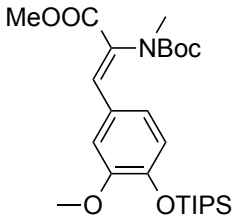
The crude acid was dissolved in DCM (3.5 ml) cooled to 0 °C. *S*-valine methyl ester hydrochloride (113 mg, 674 mmol, 1.00 eq.), HOBt (98.6 mg, 0.72 mmol, 1.20 eq.), HBTU (277 mg, 723 mmol, 1.20 eq.) and diisopropylethylamine (189 mg, 1.46 mmol, 2.20 eq.) were added. The suspension was allowed to warm to r.t. and stirred for 14 h. The reaction mixture was then diluted with EtOAc (5 mL), washed with aqueous HCl (10 mL, 1 M), saturated $NaHCO_3$ (10 mL) and brine (10 mL). After drying over sodium sulfate, filtration and subsequent removal of the solvent at reduced pressure, the residue

was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 1:1) to furnish dipeptide **S37** (274 mg, 0.43 mmol, 54% over 2 steps) as a colorless oil. $\boldsymbol{R_f}$ = 0.28 ($SiO_2$, pentane/$Et_2O$, 1:1). $\boldsymbol{[a]_D^{20}}$ = + 19.2 (c = 0.47, $CHCl_3$). **FTIR** (neat): 3382, 2944, 2867, 2358, 1743, 1675, 1606, 1585, 1513, 1463, 1395, 1282, 1236, 1211, 1154, 1037, 998, 885, 818, 767, 734, 680, 632 $cm^{-1}$. **$^1$H NMR** (400 MHz, MeOD) δ = 7.30 (m, 5H), 6.93 – 6.55 (m, 3H), 5.22 – 4.94 (m, 4H), 4.32 (d, *J* = 6.2 Hz, 2H), 3.89 – 3.65 (m, 6H), 3.19 (s, 2H), 3.01 – 2.82 (m, 4H), 2.10 (ddd, *J* = 31.3, 18.7, 4.9 Hz, 1H), 1.32 – 1.16 (m, 3H), 1.09 (d, *J* = 7.2 Hz, 18H), 0.95 – 0.85 (m, 6H). **$^{13}$C NMR** (126 MHz, MeOD) δ = 172.01, 171.99, 157.18, 150.75, 128.11, 128.0, 127.12, 120.86, 119.95, 112.57, 67.08, 66.98, 65.51, 60.06, 57.91, 57.86, 57.84, 54.34, 51.06, 47.76, 30.21, 17.93, 16.95, 12.65. **ESI-HRMS** calc. for $C_{34}H_{52}N_2NaO_7Si^+$ $[M+Na]^+$: 651.3442, found: 651.3445.

**Methyl {(*R*)-3-(3-methoxy-4-[(triisopropylsilyl)oxy]phenyl}-2-(methylamino)-propanoyl}-*S*-valinate (3.103/3.104)**: To a solution of Cbz-protected amine **S37** (129 mg, 0.20 mmol, 1.0 eq.) in MeOH (4 mL) was added Pd/C (10%, 40.0 mg, 0.32 mmol, 1.10 eq.) and after bubbling $H_2$ through the solution for 10 min, the flask was closed and kept under a hydrogen atmosphere while stirring for 2 h monitored by TLC. The mixture was filtered over a pad of diatomaceous earth and washed with DCM (20 mL). After drying over sodium sulfate, filtration and removal of the solvent, two the diastereomers **3.103** and **3.104** (91.0 mg, 0.18 mmol, 90%, ratio: 43:57) could be isolated by flash chromatography ($SiO_2$, EtOAc). Major diastereomer: $\boldsymbol{R_f}$ = 0.31 ($SiO_2$, EtOAc). $\boldsymbol{[\alpha]_D}$ = +34.8 (*c* = 1.0 $CHCl_3$). **FTIR** (neat): 3302, 3174, 2943, 2866, 2358, 1731, 1664, 1514, 1464, 1382, 1291, 1211, 1159, 1137, 1040, 1015, 908, 827, 674 $cm^{-1}$. **$^1$H NMR** (400 MHz, MeOD) δ = 6.82 – 6.75 (m, 2H), 6.69 – 6.63 (m, 1H), 4.22 (d, *J* = 5.9 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.38 (dd, *J* = 16.3, 9.4 Hz, 2H), 2.82 (d, *J* = 7.4 Hz, 2H), 2.34 (s, 3H), 2.0 (td, *J* = 13.6, 6.9 Hz, 1H), 1.33 – 1.18 (m, 3H), 1.10 (d, *J* = 7.1 Hz, 18H), 0.77 (dd, *J* = 6.9, 1.6 Hz, 6H). **$^{13}$C NMR** (101 MHz, MeOD) δ = 176.06, 173.38, 152.0, 145.53, 131.70, 122.48, 121.16, 114.42, 66.53, 59.14, 55.84, 52.42, 40.02, 34.46, 31.53, 19.43, 18.54, 18.41, 14.16. Minor diastereomer: $\boldsymbol{R_f}$ = 0.34 ($SiO_2$, EtOAc). $\boldsymbol{[\alpha]_D}$ = –28.6 (*c* = 1.0 $CHCl_3$). **FTIR** (neat): 3341, 2944, 2867, 2352, 1743, 1673, 1605, 1512, 1464, 1280, 1235, 1157, 1037, 1016, 883, 816, 757, 678 $cm^{-1}$. **$^1$H NMR** (500 MHz, MeOD) δ = 6.79 – 6.72 (m, 2H), 6.63 (dd,

*J* = 8.0, 2.1 Hz, 1H), 4.31 (d, *J* = 6.2 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.48 – 3.31 (m, 1H), 2.90 – 2.74 (m, 2H), 2.31 (s, 3H), 2.11 – 2.03 (m, 1H), 1.30 – 1.17 (m, 3H), 1.08 (d, *J* = 7.3 Hz, 18H), 0.89 (d, *J* = 6.8 Hz, 6H). **$^{13}$C NMR** (126 MHz, MeOD) δ = 175.89, 172.97, 152.05, 131.76, 122.45, 121.24, 114.28, 66.91, 58.90, 55.74, 52.53, 40.13, 34.74, 31.98, 19.49, 18.47, 18.39, 14.13. **ESI-HRMS** calc. for $C_{26}H_{46}N_2NaO_5Si^+$ $[M+Na]^+$: 517.3074, found: 517.3068.

**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(triisopropyl-silyl)oxy]phenyl}acrylate** (**S38**): The carbamate **3.98** (311 mg, 0.65 mmol, 1.0 eq.) was dissolved in DMF (5 mL) and cooled to 0 °C. NaH (31.0 mg, 0.77 mmol, 1.20 eq., 60% dispersion in mineral oil) was added and stirring was continued for 10 min before MeI (368 mg, 2.59 mmol, 4.0 eq.) was added drop wise. The reaction mixture was allowed to warm to r.t. and after 1.5 h was quenched with saturated aqueous $NH_4Cl$ (20 mL). The suspension was extracted with $Et_2O$ (3 x 20 mL) and the combined organic layers were washed with $H_2O$ (4 x 50 mL) before drying over sodium sulfate. After removal of the solvent, the residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:2) to furnish methylated product **S38** (273 mg, 0.55 mmol, 86%) as a slightly yellow oil. $\boldsymbol{R_f}$ = 0.31 ($SiO_2$, pentane/$Et_2O$, 3:2). **FTIR** (neat): 2945, 2867, 2360, 1715, 1635, 1596, 1512, 1463, 1434, 1347, 1285, 1228, 1153, 1069, 1037, 1009, 901, 819, 776, 681 $cm^{-1}$. **$^1$H NMR** (250 MHz, $CDCl_3$) δ= 7.29 (s, 1H), 7.16 – 7.08 (m, 1H), 7.05 – 6.96 (m, 1H), 6.91 – 6.82 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.96 (s, 3H), 1.35 (s, 9H), 1.29 – 1.17 (m, 3H), 1.09 (d, *J* = 6.7 Hz, 18H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 166.39, 155.10, 150.89, 147.53, 134.46, 128.91, 126.41, 124.17, 120.39, 112.71, 80.31, 55.15, 52.04, 34.30, 28.14, 17.69, 12.71. **ESI-HRMS** calc. for $C_{26}H_{43}NNaO_6Si^+$ $[M+Na]^+$: 516.2758, found: 516.2752.



**Methoxymethyl (*R*)-2-(methoxymethoxy)-2-phenylacetate** (**S39**):[320] (*R*)-(–)-mandelic acid (**3.82**) (2.00 g, 10.0 mmol, 1.0 eq.) was dissolved in dry DCM (25 ml). DIPEA (5.43 ml, 30.0 mmol, 3.0 eq.) was added followed by chloromethyl methyl ether (2.50 ml, 30 mmol, 3.00 eq.) upon which the formation of HCl gas could be observed. The mixture was gently refluxed for 18 h. The mixture was then washed with water (3 x 50 mL). The organic layer was dried over Sodium sulfate and filtered before removal of the solvent. The crude product was further purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 4:1) to obtain compound **S39** (2.91 g, 0.01 mmol, 93%) as a colorless oil. All analytical data were in full agreement with the literature data. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.51 – 7.46 (m, 2H), 7.41 – 7.32 (m, 3H), 5.26 (dd, *J* = 20.7, 5.9 Hz, 2H), 5.20 (s, 1H), 4.74 (dd, *J* = 26.2, 6.9 Hz, 2H), 3.40 (s, 3H), 3.29 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 170.53, 136.13, 128.97, 128.83, 127.60, 95.18, 91.04, 57.68, 56.16.

**(*R*)-2-(Methoxymethoxy)-2-phenylacetaldehyde** (**3.83**):[320] To a -78 °C cold solution of ester **S39** (1.0 g, 4.18 mmol, 1.0 eq.) in dry DCM (10 ml) was slowly added DIBAL-H (4.60 ml, 4.60 mmol, 1.10 eq., 1 M in cyclohexane). The solution was stirred at -78 °C for 2 h and then quenched with MeOH (10 mL). The mixture was then allowed to warm to r.t. and the viscous suspension filtered over a pad of diatomaceous earth. The residue was washed with $H_2O$ (20 ml) and extracted with DCM (50 ml) and the aqueous phase was extracted with DCM (3 x 30 ml). The combined organic layers were dried over sodium sulfate and the solvent removed at reduced pressure. The residue was purified by flash chromatography ($SiO_2$, pentane/ether, 3:2) to obtain the MOM-protected ester **3.83** (572 mg, 3.17 mmol, 76%) as a colorless and semi stable oil (5% decomposition after storage for 4 weeks at -20 °C). All analytical data were in full agreement with the literature data. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.62 (d, *J* = 1.6 Hz, 1H), 7.50 – 7.32 (m, 5H), 5.04 (s, 1H), 4.85 – 4.68 (m, 2H), 3.42 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 198.01, 133.67, 129.18, 129.10, 127.76, 95.36, 83.31, 56.15.

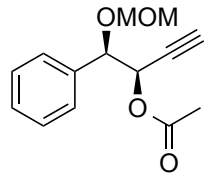
[320] E. J. Corey, F. J. Hannon, N. W. Boaz, *Tetrahedron* **1989**, *45*, 545.

**(1*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-ol** (**3.84**): The aldehyde **3.83** (1.52 g, 8.47 mmol, 1.0 eq.) was dissolved in dry THF (15 mL) and cooled to -78 °C. Then ethynylmagnesium bromide (25.4 mL, 12.7 mmol, 1.5 eq., 0.5 M solution in THF) was added drop wise and the reaction stirred for 1 h while slowly warming to room temperature. The mixture was then quenched with saturated aqueous $NH_4Cl$ (30 mL) and extracted with $Et_2O$ (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and after removal of the solvent purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 2:3) to furnish the propargylic alcohol **3.84 (**1.41 g, 6.82 mmol, 81%, d.r.: 3:2 *syn*/*anti*) as a colorless oil. $R_f$ = 0.25 ($SiO_2$, pentane/$Et_2O$ 2:3). **FTIR** (neat): 3412, 3288, 3033, 2951, 2983, 2827, 2681, 2334, 2118, 1605, 1454, 1403, 1262, 1212, 1150, 1073, 1025, 916, 846, 762, 703, 632 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.47 – 7.30 (m, 5H), 4.79 – 4.60 (m, 3H), 4.52 (dd, *J* = 6.5, 1.6 Hz, 1H), 3.44 (d, *J* = 27.2 Hz, 3H), 2.93 (d, *J* = 13.3 Hz, 1H), 2.43 (dd, *J* = 29.9, 2.2 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 137.0, 136.91, 128.74, 128.55, 128.45, 128.10, 127.62, 95.74, 94.87, 82.23, 81.50, 81.03, 75.07, 74.87, 66.77, 66.53, 56.18, 56.10. **ESI-HRMS** calc. for $C_{12}H_{14}NaO_3^+$ $[M+Na]^+$: 229.0841, found: 229.0853.

**(1*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-yl 3,5-dinitrobenzoate** (**S40**): To a solution of diastereomeric mixture of the propargylic alcohol **3.84** (104 mg, 500 µmol, 1.0 eq.) in dry DCM (2 mL) were added 3,5-dinitrobenzoyl chloride (237 mg, 1.01 mmol, 2.0 eq.), DMAP (6.15 mg, 50 mmol, 0.10 eq.) and $NEt_3$ (128 mg, 1.26 mmol, 2.50 eq.), upon which the formation of HCl gas could be observed. The clear red solution was stirred for 14 h, quenched with saturated aqueous $NH_4Cl$ (5 mL) and extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were dried over sodium sulfate and the residue was purified by flash chromatography ($SiO_2$, pentane/$Et_2O$ 3:1) to furnish the ester **S40** (159 mg, 0.39 mmol, 79%) as a yellowish oil. $R_f$ = 0.36 ($SiO_2$, pentane/ether 3:1). **FTIR** (neat): 3472, 3288, 3100, 2952, 2893, 2826, 2359, 2129, 1983, 1738, 1629, 1600, 1544, 1495, 1458, 1343, 1267, 1155, 1102, 1076, 1024, 966, 844, 767, 720, 647, 610 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.24 (dt, *J* = 9.9, 2.1 Hz, 1H), 9.14 (dd, *J* = 35.8, 2.1 Hz, 2H), 7.58 – 7.33 (m, 5H), 7.24 – 7.13 (m, 1H), 5.88 (ddd, *J* = 7.0, 6.0, 2.2 Hz, 1H), 5.06 (dd, *J* = 8.9, 6.0 Hz, 1H), 4.75 – 4.58 (m,

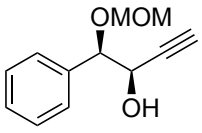
2H), 3.41 (d, *J* = 26.2 Hz, 3H), 2.57 (dd, *J* = 47.7, 2.2 Hz, 1H), 2.36 (s, 1H).**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 161.48, 148.86, 135.93, 135.79, 133.45, 129.74, 129.72, 129.28, 129.18, 128.73, 128.68, 128.37, 128.22, 128.01, 125.44, 122.86, 94.71, 94.59, 78.11, 77.93, 77.06, 68.88, 56.05. **ESI-HRMS** calc. for $C_{19}H_{16}N_2NaO_8^+$ $[M+Na]^+$: 423.0805, found: 423.0799.

**(1*R*,2*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-yl acetate** (**3.91**): The




diastereomerically impure alcohol **3.84** (956 mg, 4.64 mmol, 1.0 eq.) was dissolved in dry hexane (20 mL) and vinyl acetate (1.39 g, 16.2 mmol, 3.50 eq.) and immobilized lipase B from *Candida antarctica* (50 mg, >2 U/mg) were added. The mixture was stirred for 6 d, upon which $^1$H NMR indicated complete consumption of one of the diastereomeric alcohols. The suspension was filtered and the solvents removed. The residue was then purified by flash chromatography ($SiO_2$, pentane/$Et_2O$, 3:2) to obtain the ester **3.91** (580 mg, 2.34 mmol, quant.) as a diastereomerically pure compound. $\boldsymbol{R_f}$ = 0.31 ($SiO_2$, pentane/$Et_2O$ 3:2). $\boldsymbol{[\alpha]_D}$ = –185 (*c* = 0.85 $CHCl_3$). **FTIR** (neat): 3285, 2946, 2893, 1744, 1454, 1372, 1226, 1152, 1104, 1021, 971, 918, 831, 765, 703, 633 $cm^{-1}$. **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.46 – 7.33 (m, 5H), 5.67 (dd, *J* = 6.7, 2.2 Hz, 1H), 4.86 (d, *J* = 6.7 Hz, 1H), 4.63 (dd, *J* = 25.3, 6.8 Hz, 2H), 3.41 (s, 3H), 2.41 (d, *J* = 2.2 Hz, 1H), 2.13 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 169.67, 136.59, 128.84, 128.43, 128.23, 94.55, 78.63, 78.12, 75.44, 66.53, 55.86, 20.98. **ESI-HRMS** calc. for $C_{14}H_{16}NaO_4^+$ $[M+Na]^+$: 271.0938, found: 271.0941.

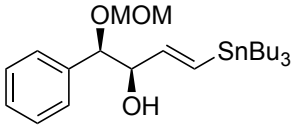
**(1*R*,2*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-ol** (**3.92**): To a solution of the ester




**3.91** (330 mg, 1.33 mmol, 1.0 eq.) in a mixture of MeOH (2.4 mL) and water (0.6 mL) was added $K_2CO_3$ (919 mg, 6.65 mmol, 5.0 eq.). After 1 h stirring at room temperature, TLC indicated full consumption of the starting material and the mixture was acidified with aqueous HCl (1 M). The mixture was then extracted with $Et_2O$ (3 x 20 mL) and the combined organic layers were dried over sodium sulfate. Evaporation of the solvent under reduced pressure furnished (1*R*,2*R*)-1-(methoxymethoxy)-1-phenylbut-3-yn-2-ol (**3.92**) (256 mg, 1.24 mmol, 94%) as a colorless oil. $\boldsymbol{R_f}$ = 0.25 ($SiO_2$, pentane/$Et_2O$ 2:3). $\boldsymbol{[\alpha]_D}$ = –155.7 (*c* = 0.85 $CHCl_3$).

**FTIR** (neat): 3412, 3288, 3033, 2951, 2983, 2827, 2681, 2334, 2118, 1605, 1454, 1403, 1262, 1212, 1150, 1073, 1025, 916, 846, 762, 703, 632 $cm^{-1}$. **$^{1}$H NMR** (500 MHz, $CDCl_3$) δ = 7.42 – 7.32 (m, 5H), 4.71 – 4.65 (m, 2H), 4.64 – 4.61 (m, 1H), 4.52 (dd, *J* = 6.8, 2.1 Hz, 1H), 3.41 (s, 3H), 2.81 (s, 1H), 2.40 (d, *J* = 2.2 Hz, 1H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 137.0, 128.76, 128.47, 128.10, 94.89, 81.49, 81.05, 74.88, 66.56, 56.12. **ESI-HRMS** calc. for $C_{12}H_{14}NaO_3^+$ $[M+Na]^+$: 229.0841, found: 229.0852.

**(1*R*,2*R*,*E*)-1-(Methoxymethoxy)-1-phenyl-4-(tributylstannyl)but-3-en-2-ol** (**3.27**):




To a solution of the alkyne **3.92** (96 mg, 460 mmol, 1.0 eq.) in dry THF (5 mL) was added bis(triphenylphosphine)palladium(II) chloride (16.3 mg, 20.0 µmol, 5 mol%) at 0 °C. Then tributyltin hydride (0.21 ml, 0.69 mmol, 1.50 eq.) was added slowly. After 30 min TLC indicated complete consumption of the starting material. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($SiO_2$, $Et_2O$/pentane/$NEt_3$ 2:3:0.05) to yield the stannane **3.27** (132 mg, 265 mmol, 58%, *E*/*Z* >10:1) as a dark brownish oil. The stannane should be used immediately as it decomposes within 2 weeks at 5 °C to an unknown byproduct in a 1:1 ratio. $\boldsymbol{R_f}$ = 0.34 ($SiO_2$, $Et_2O$/pentane/$NEt_3$ 2:3:0.1). **$[a]_D^{20}$** = –29.8 (*c* = 0.39 $CHCl_3$). **FTIR** (neat): 3465, 2924, 2851, 1603, 1456, 1376, 1341, 1255, 1150, 1074, 1025, 921, 864, 755, 700, 664 $cm^{-1}$. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 7.36 – 7.27 (m, 5H), 6.12 (dd, *J* = 19.2, 1.4 Hz, 1H), 5.78 (dd, *J* = 19.2, 5.3 Hz, 1H), 4.60 (d, *J* = 0.7 Hz, 2H), 4.43 (d, *J* = 7.5 Hz, 1H), 4.30 – 4.22 (m, 1H), 3.38 (s, 3H), 2.87 (d, *J* = 2.9 Hz, 1H), 1.48 – 1.18 (m, 14H), 0.96 – 0.70 (m, 16H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 145.24, 138.14, 131.48, 128.37, 128.29, 128.13, 94.69, 82.44, 78.52, 56.03, 29.12, 27.42, 13.82, 9.49. **ESI-HRMS** calc. for $C_{24}H_{42}NaO_3Sn^+$ $[M+Na]^+$: 521.2054, found: 521.2052.

**Preparation of the (*S*)- and (*R*)-MTPA-diol esters 3.93 and 3.94 :** To a stirred solution of the alcohol **3.92** (10 mg, 40.3 mmol, 1.0 eq.) and dry pyridine (11.9 mg, 150 mmol, 3.1 eq.) in dry DCM (1 mL) was added (*R*)-(–)-MTPACl (23.3 mg, 90.0 mmol, 1.90 eq.) at room temperature. After stirring for 15 h, the mixture was quenched by the addition of $H_2O$ (1 mL) and extracted with $Et_2O$ (3 x 5 mL). The combined organic layers were dried over sodium sulfate and after removal of the solvent, the crude product was further purified by flash chromatography ($SiO_2$, $Et_2O$/pentane, 2:3) to give the *S*-ester **3.94** as a colorless oil (20 mg, 40.0 µmol, 98%). **$^1$H NMR** (600 MHz, $CDCl_3$) δ = 7.58 – 7.54 (m, 2H), 7.44 – 7.36 (m, 3H), 7.35 – 7.30 (m, 5H), 5.79 (dd, *J* = 7.9, 2.2 Hz, 1H), 4.75 (d, *J* = 7.9 Hz, 1H), 4.38 (dd, *J* = 14.8, 6.8 Hz, 2H), 3.62 (d, *J* = 1.0 Hz, 3H), 3.01 (s, 3H), 2.42 (d, *J* = 2.2 Hz, 1H).

In an entirely analogous fashion, the (*R*)-ester **3.93** was prepared using (*S*)-(+)-MTPACl with a yield of 95%. **$^1$H NMR** (600 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 6.9 Hz, 2H), 7.45 – 7.33 (m, 12H), 5.74 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.85 (d, *J* = 8.2 Hz, 1H), 4.60 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 3.54 (d, *J* = 0.6 Hz, 3H), 3.42 (d, *J* = 1.1 Hz, 2H), 3.24 (s, 3H), 2.38 (d, *J* = 2.2 Hz, 1H).

# 6 Acknowledgements

During the course of my PhD, I have had the pleasure to meet many inspiring people and make new friends, to whom I would like to express my gratitude here.

I would like to thank my Doktorvater Prof. Dr. *Karl Gademann* for inviting me to the Gademann-group-family! Your passion for organic chemistry and your encouragement have turned obstacles into stepping-stones for me more than once. I would also like to thank you for you personal advice, from my driving lessons to the secrets of midnight-diaper changing and related fields. I wish you all the best for your appointment in Zürich.

I am much obliged to Prof. Dr. *Andreas Pfaltz* for accepting the coexamination of this Thesis. Your lecture on modern synthetic methods has encouraged me to further focus my studies on synthetic organic chemistry.

This manuscript has been greatly improved by the grace of my proof reading colleagues Dr. *Erika Crane*, Dr. *Regina Berg*, *Elias Kaufmann* and *Robin Wehlauch*. For the latter two I hope that you will find equally talented lectors for your theses.

I am thankful for the several Wahlpraktikum students I have supervised who contributed to this work. Special credit goes to *Chris Wittwer* who contributed substantially to the aetheramide B project and with whom I had a great time. Weiter so, mein Junge!

Our collaboration with the Pfaltz group has proven fruitful several times. I would like to thank the group members for their kind technical advice and support and especially Dr. *Maurizio Bernasconi* for the collaboration and good times on the pyridovericin project.

I also had the pleasure to work with Dr. *Patrick Burch* on several occasions and I would like to thank him for his efforts on the neuritogenic surface project and his honest and cheerful attitude.

I would like to thank “the great old ones” Dr. *Henning Jessen*, Dr. *Johannes David Hoecker*, Dr. *José Zurbriggen-Gomes*, Dr. *Vreni Grundler,* Dr. *Samuel Bernd Bader* and Dr. *Malika Makhlouf Brahmi* for making my start in the group so much enjoyable.

My thanks also go to the many great post-docs I had the pleasure to work with, especially Dr. *Hideki Miyatake Ondozal* and Dr. *Suman de Sarkar* for sharing their "great mirror wisdom".

My lab mates from laboratory 102 made my PhD so much more enjoyable. Dear *Simon*, I've always admired your non-conformist approach to problem solving and your ability to find a well-hidden product in the chromatogram, like a 50% article in a sea of 20% off-articles. Dear *Röbi*, for ten kalpas I've studied Gutei's one finger Zen, while all the time I had a master sitting next to me. Let me thank you with a poem:

"*A lonely hut on the mountain-peak towering above a thousand others;*
*One half is occupied by an old monk and the other by a cloud.*
*Last night it was stormy and the cloud was blown away;*
*After all a cloud could not equal the old man's quiet way*."

Laboratory 101 was always my first destination when on sabbatical from lab 102. Dear *Lisu*, I greatly admire your ability to keep a positive attitude while tasting the bittersweet side of sugar chemistry. Looks like it paid off! Dear *Erika*, you are my favorite American (after G. W. B. Jr. and Collin)! I wish you all the best for your new life with your family, may peace and blessings be upon you.

After my sabbaticals in 101, I usually visited lab 104 and watched "*the drama unfold"*. Dear *3000 registered chemicals-Spliffert*, life is change, life is chaos. All these chemicals will eventually become carbon dioxide, but your mind is free. All the best to you! Dear *mother hen Isabel*, you are doing a great job in the lab and also with your delicate group job. I think you could allow yourself a break from the latter from time to time, you've earned it! Cher *chasseur du pigeon Christophe*, we started together, hang in there together, and got out there together. Let me share this poem with you:

"*Pigeon, oiseau à la grise robe, Dans l'enfer des villes*
*À mon regard tu te dérobes , Tu es vraiment le plus agile*."

My thanks also go to Dr. *Regina Berg* who inherited our ever-giving pyridone project. I've always enjoyed your adroitness in literature and your positive spirit.

Usually people stop at two pages of acknowledgements, but I'll just keep going and see where this goes.

My comrades in lab 106 always put that smile back on my face when I returned empty handed from the *Materialausgabe*. Dear *Daeppen*, you'll be fine, just go with the flow. And don't go to Palma (or Vegas). Dear *Fischer*, I've never had the chance to tell you just how much I… oh… no- wait! Aaaaah I was too slow now he's gone. Just take it slow brother! You might miss the gentle touch of the golden breeze on an autumn day.

Of course I would also like to thank all the other former and newer members of the group, and I hope you'll have a great time in the group with the chemistry and with your bench, lab, and group mates.

I am really happy to have met my recent acquaintances *Trane, Miles, Wayne Shorter, Bill Evans, Julian 'Cannonball' Adderley, Herbie Hancock* and them other cats. Just when I thought I heard it all, you came and blew my mind. Thank you. Of course I have to thank the other people who helped me to express myself throughout the years, especially *Tom Keenig,* the *Garcia brothers* and *Luca 'Cool Hand Luke' Skywalker-Glausen*.

I have always enjoyed the time with my friends *Max Hurter*, *Mike Schneitter* and my brother up north *Gregor Meier.* The cold night on the 'bald mountain'- west face of Lhotse- will always be remembered. Greetings go to my Kazakh friend Виктор Хоффман, and always Еркіндік қыраны шарықта, Елдікке шақырып тірлікте!

My dear friends at the *Sunshine Ranch,* you have been a great source of inspiration throughout the last years. I wish you all the best for your journeys!

Dear *Noe*, *Eva* and *Mel* (just like methyl iodide), you have turned the unforeseen disbandment of my former housing project into a great time in our new flat. Life has many high high points and some less high high points (getting optimistic in here), and with you I enjoyed some of the highest highs, thank you!

My greetings go to the admirable teachers of the great way, especially *Bodhidharma*, *Jōshū*, *Nansen, Baso* and one-finger *Gutei* for pacifying the mind.

I also want to thank my father, for he would have let me borrow one of his suits for my defense. I didn't try the suit, and it probably would not have fit very well. Still I appreciate the gesture. But man cannot always rely on other people's suit, so I bought my own suit. It suits me just fine. I hope you like it!

Dear *Assja*, what can I say! I would like to thank you for all your passion, patience and love that you continually invest to keep this little thing of ours going. I'm looking forward to travel with you in our yellow bus and the many things we will see. Let me share this Koan with you:

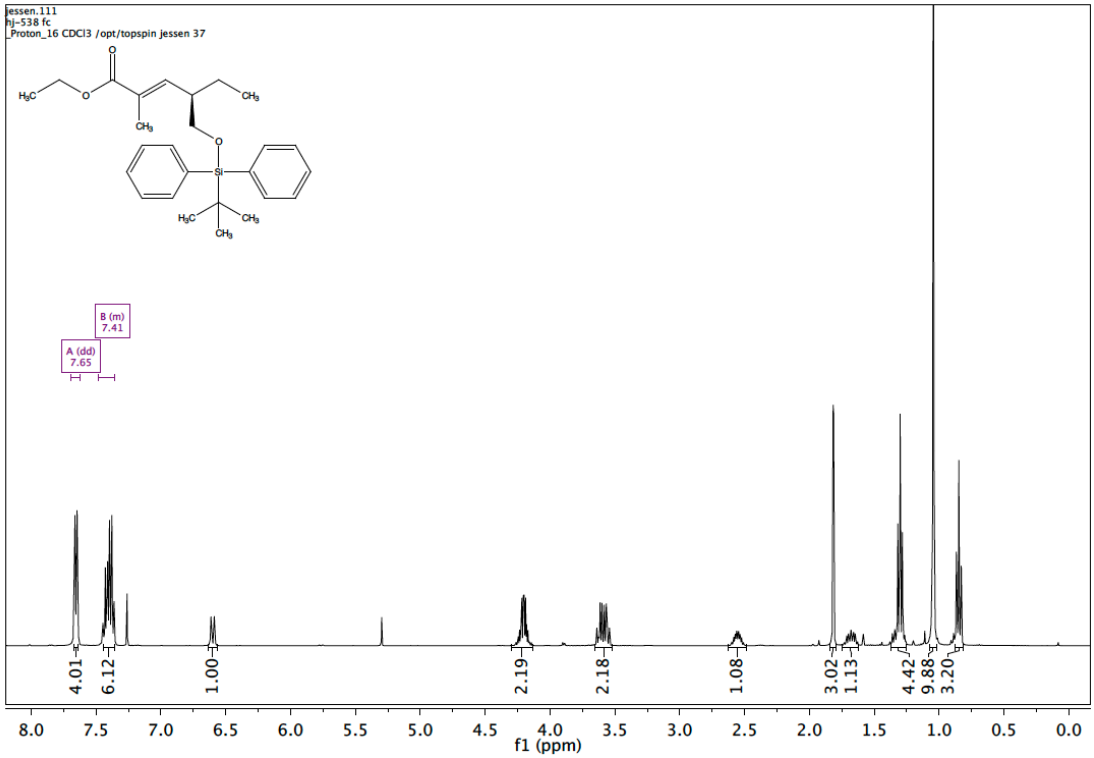
*A monk said to Hōgen "My name is Echō. I ask you, what is the Buddha?" Hōgen Said, "You are Echō."*

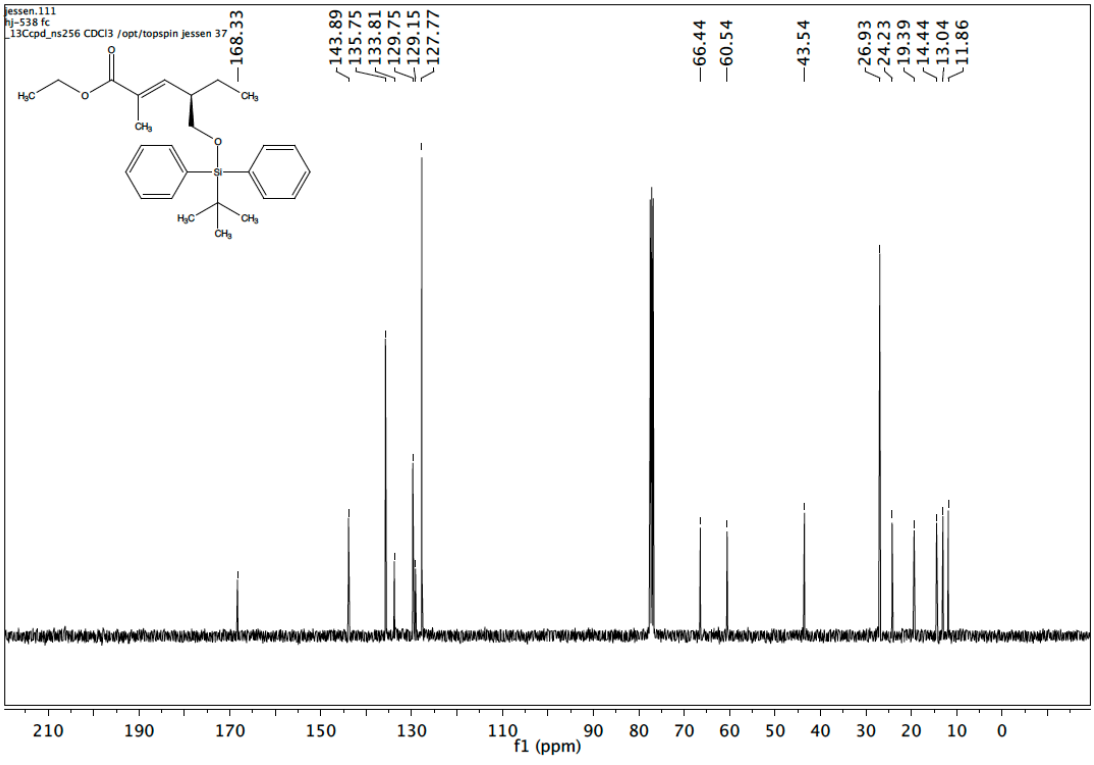
Dear *Noah*, I am so happy that you came into our life. I just read that the universe is 13 billion years old and 93 billion light years long, but you just came at the right time and place! This last Koan is for you:

*Nansen pointed to a flower in the garden, called Taifu to him, and said, "People of these days see this flower as though they were in a dream."*

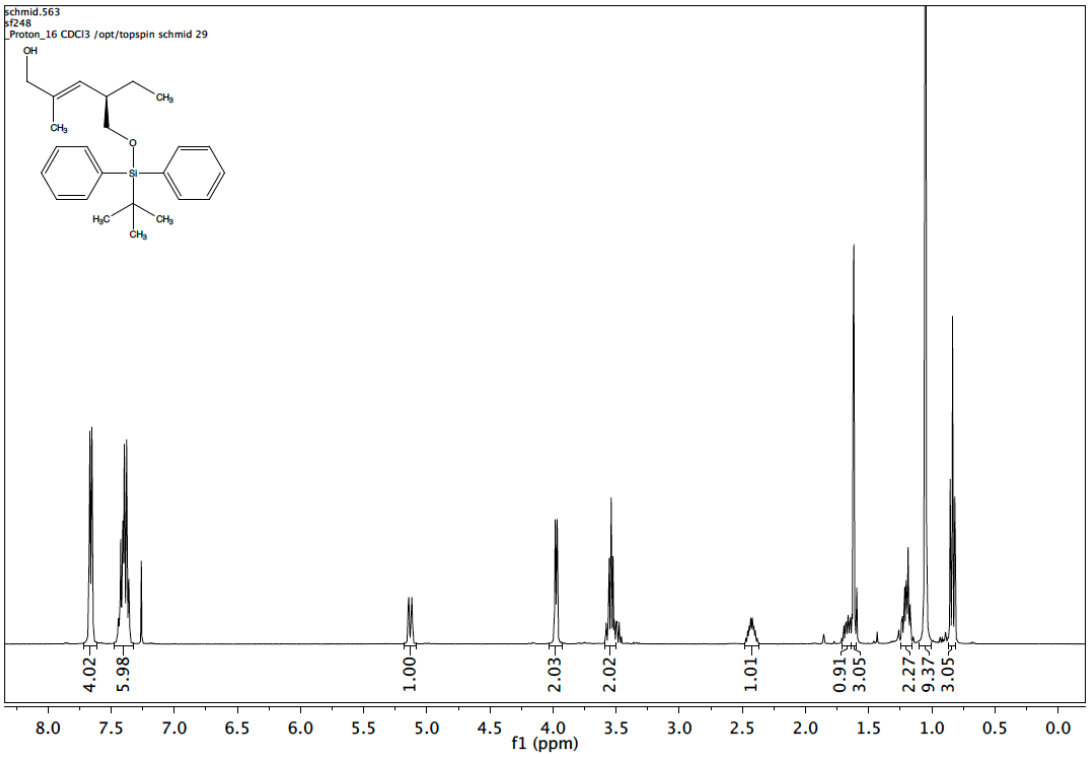
# 7 NMR Spectra

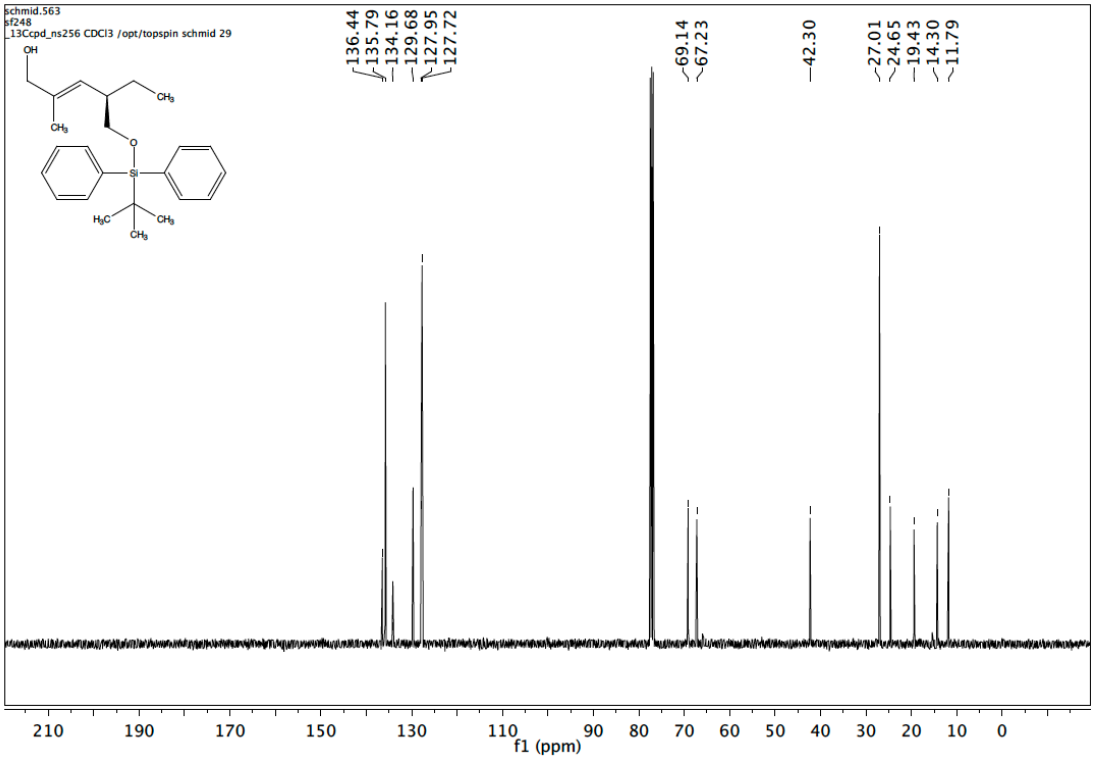
**(*R*,*E*)-ethyl-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhex-2-enoate (2.71):**



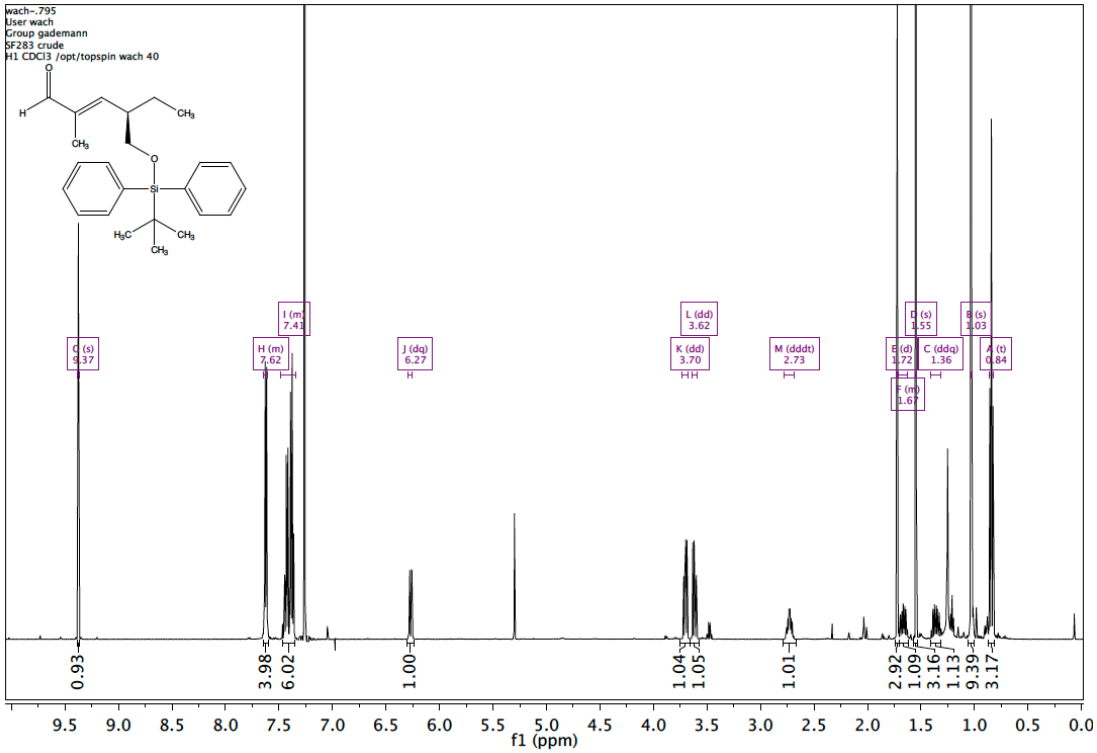



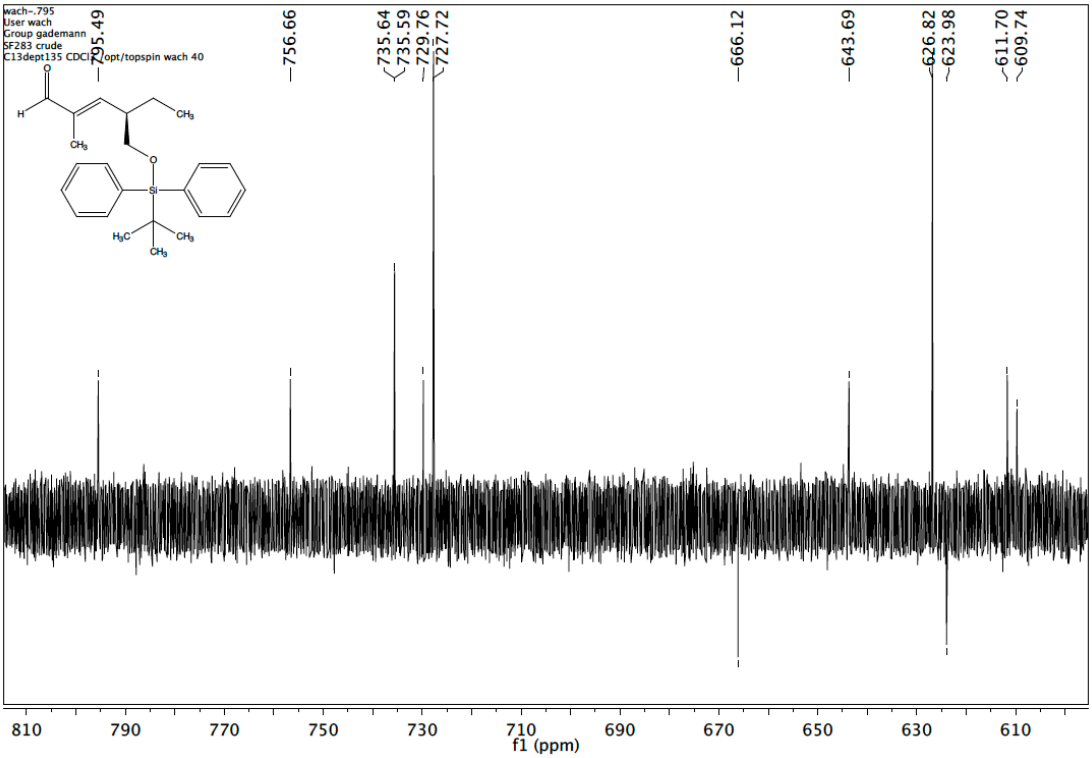
**(*R*,*E*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhex-2-en-1-ol (S2):**

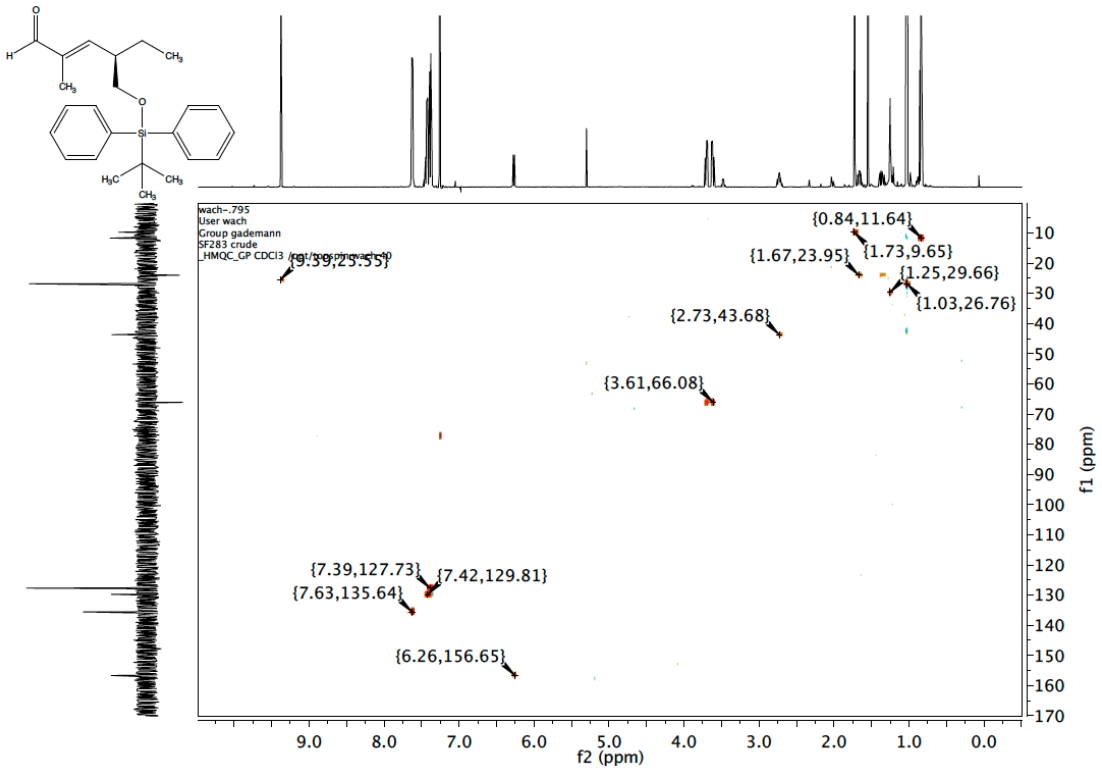


**(*R*,*E*)-4-(hydroxymethyl)-2-methylhex-2-enal (S3):**




wach~.795
User wach
Group gademann
SF283 crude
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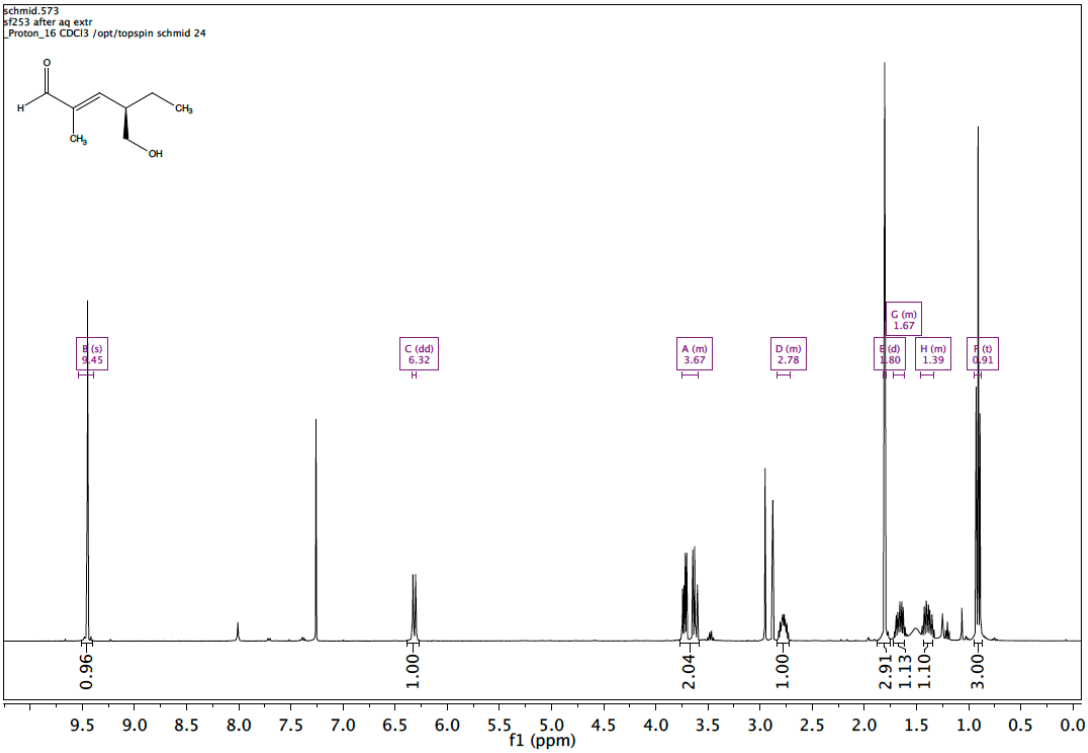
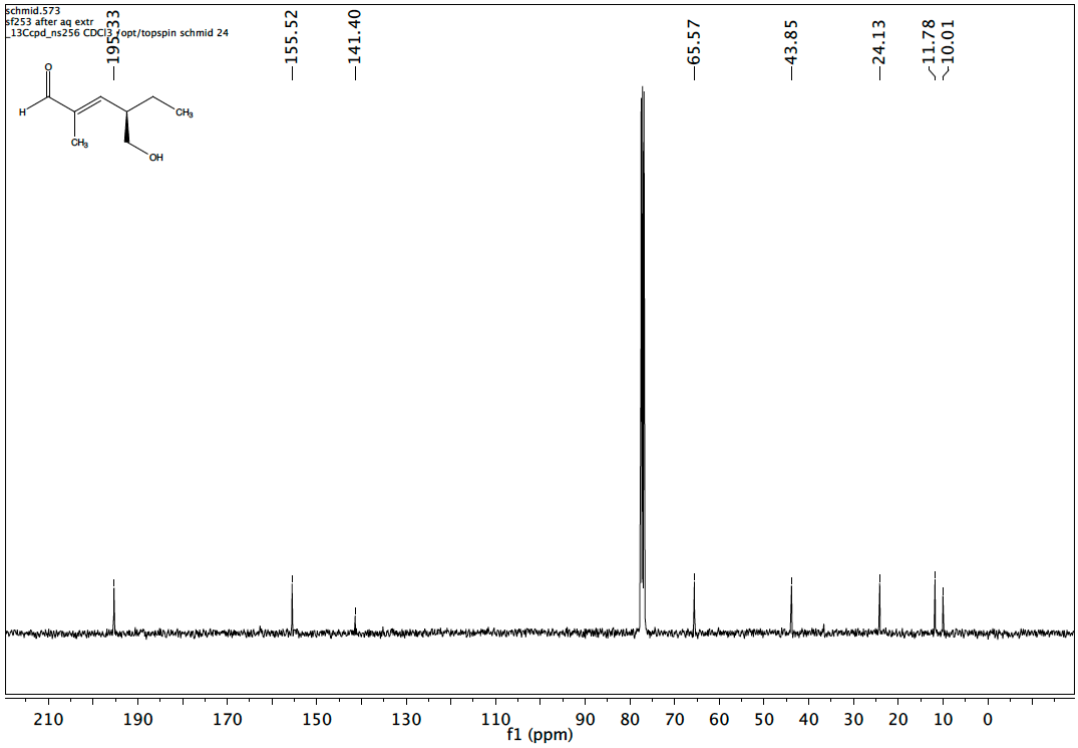
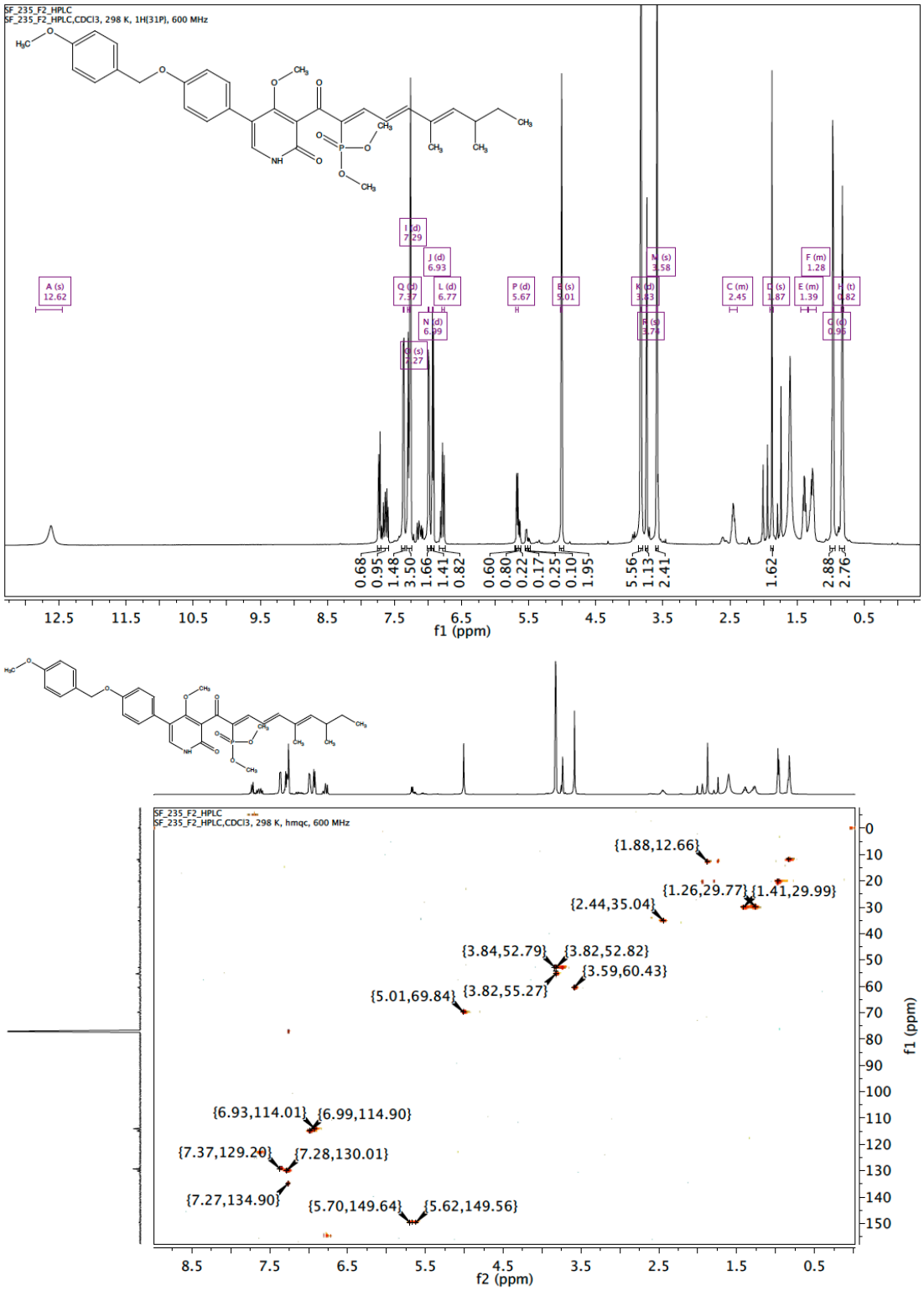
f2 (ppm)
f1 (ppm)

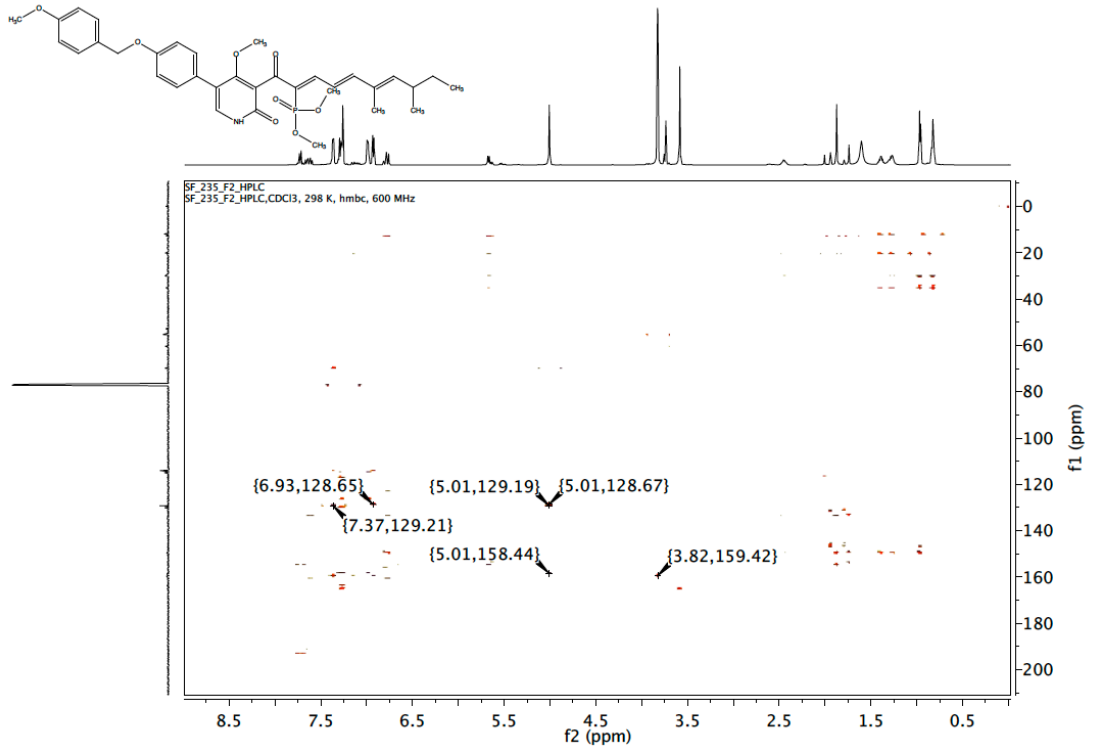
**(*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)butanal (S1):**

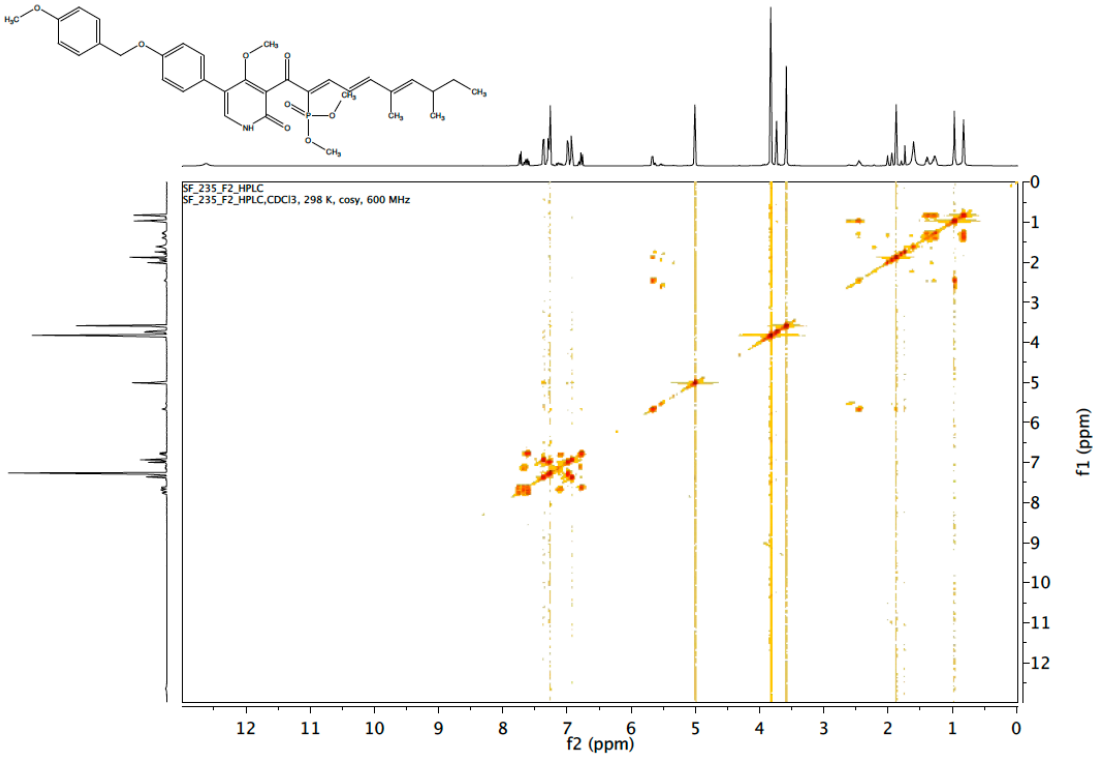


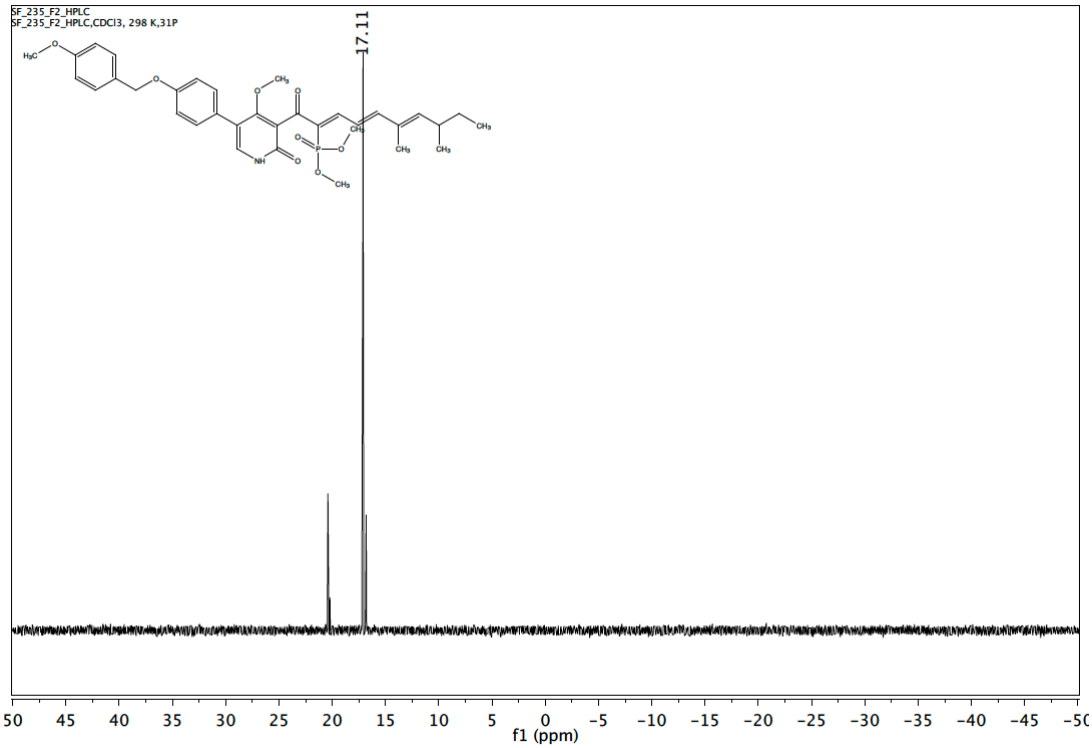



**Dimethyl ((2*Z*,4*E*,6*E*)-1-(4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)-6,8-dimethyl-1-oxodeca-2,4,6-trien-2-yl)phosphonate (2.74):**

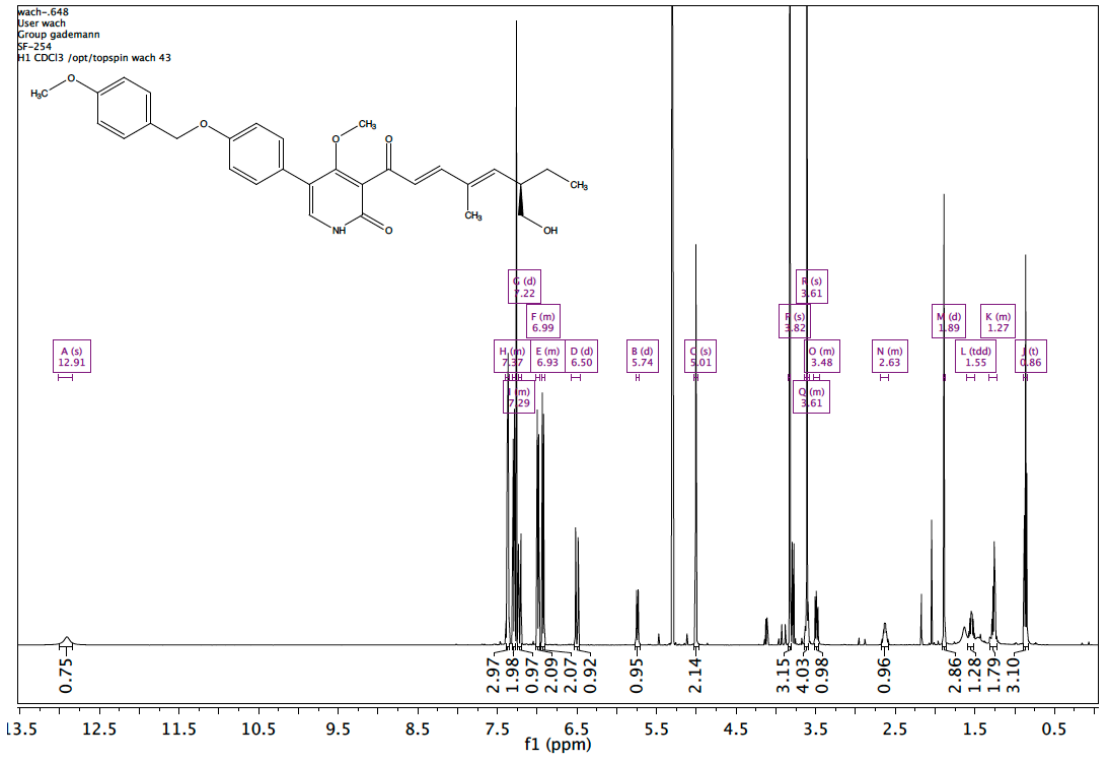


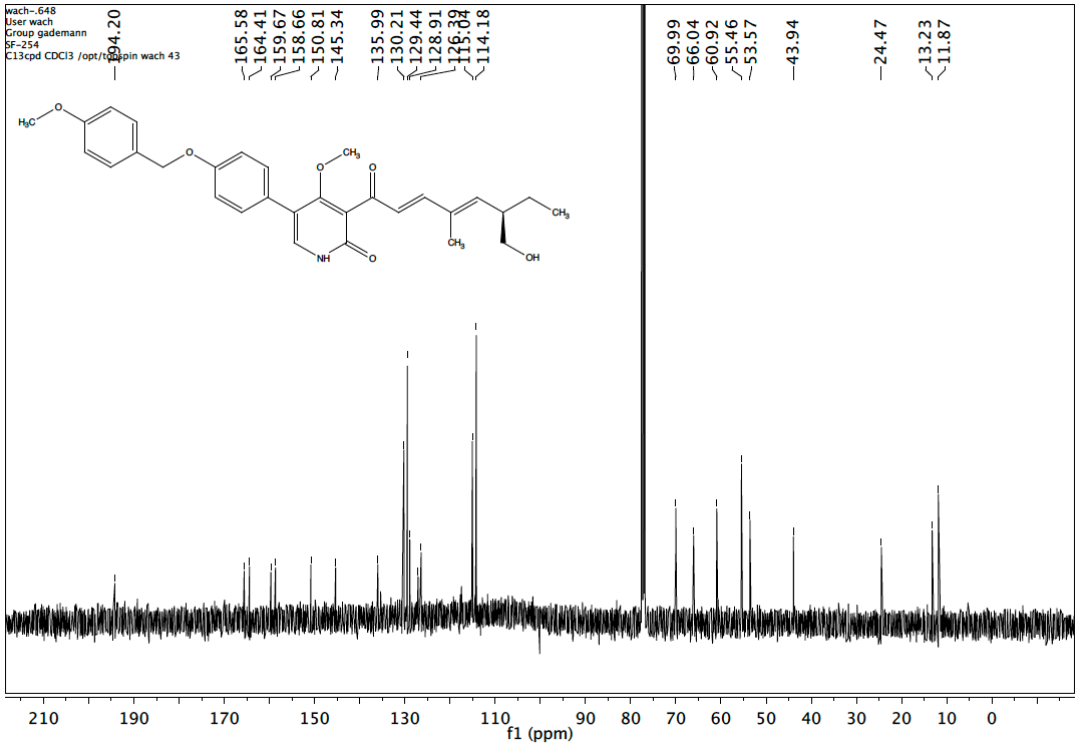

SF_235_F2_HPLC
SF_235_F2_HPLC,CDCl3, 298 K, hmbc, 600 MHz
{6.93,128.65}
{5.01,129.19}
{5.01,128.67}
{7.37,129.21}
{5.01,158.44}
{3.82,159.42}
f2 (ppm)
f1 (ppm)

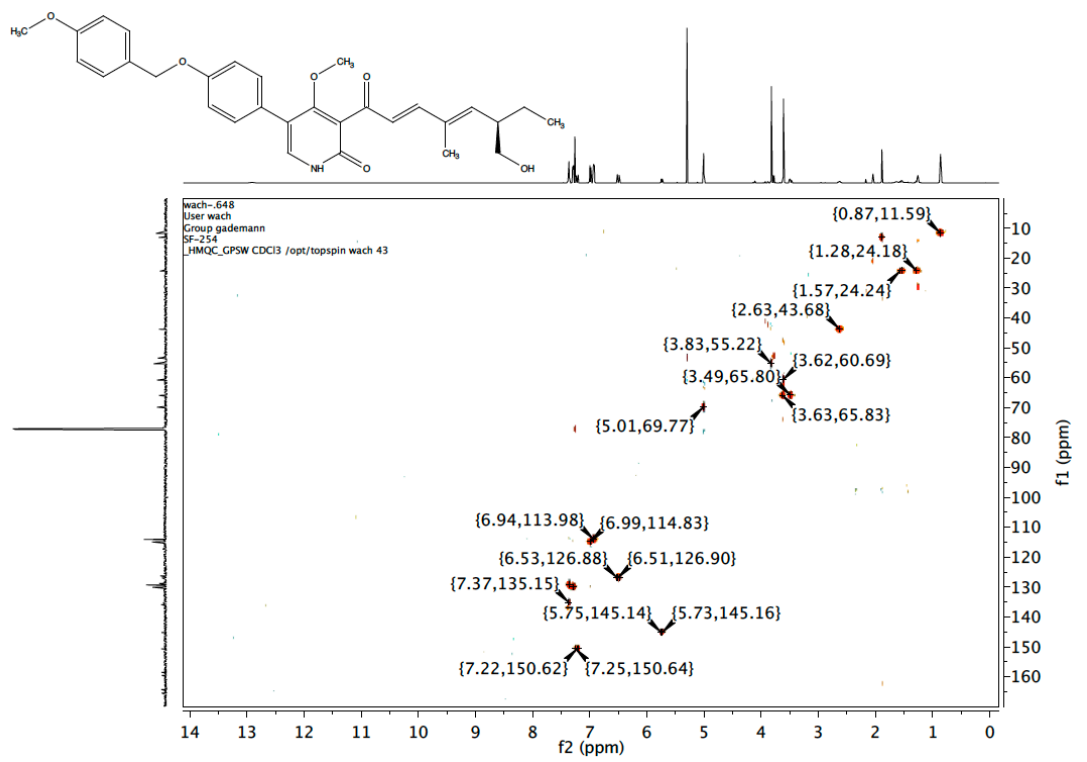

SF_235_F2_HPLC
SF_235_F2_HPLC,CDCl3, 298 K, cosy, 600 MHz
f2 (ppm)
f1 (ppm)

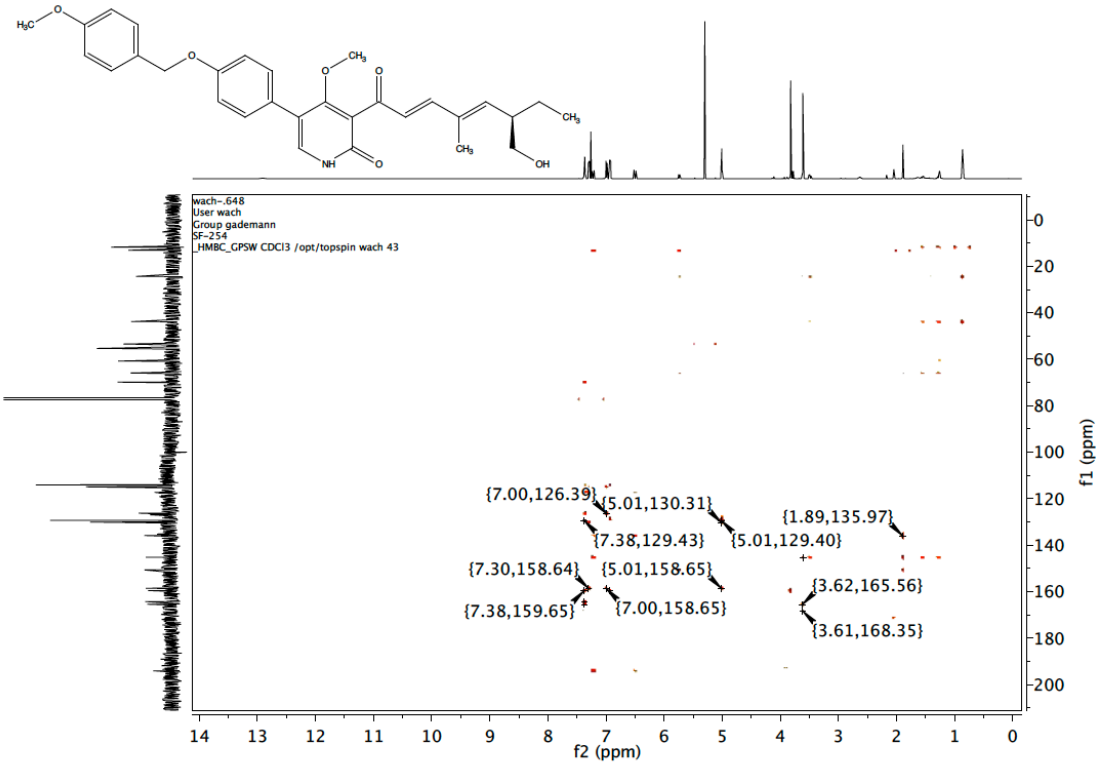

SF_235_F2_HPLC
SF_235_F2_HPLC,CDCl3, 298 K,31P
17.11
50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50
f1 (ppm)

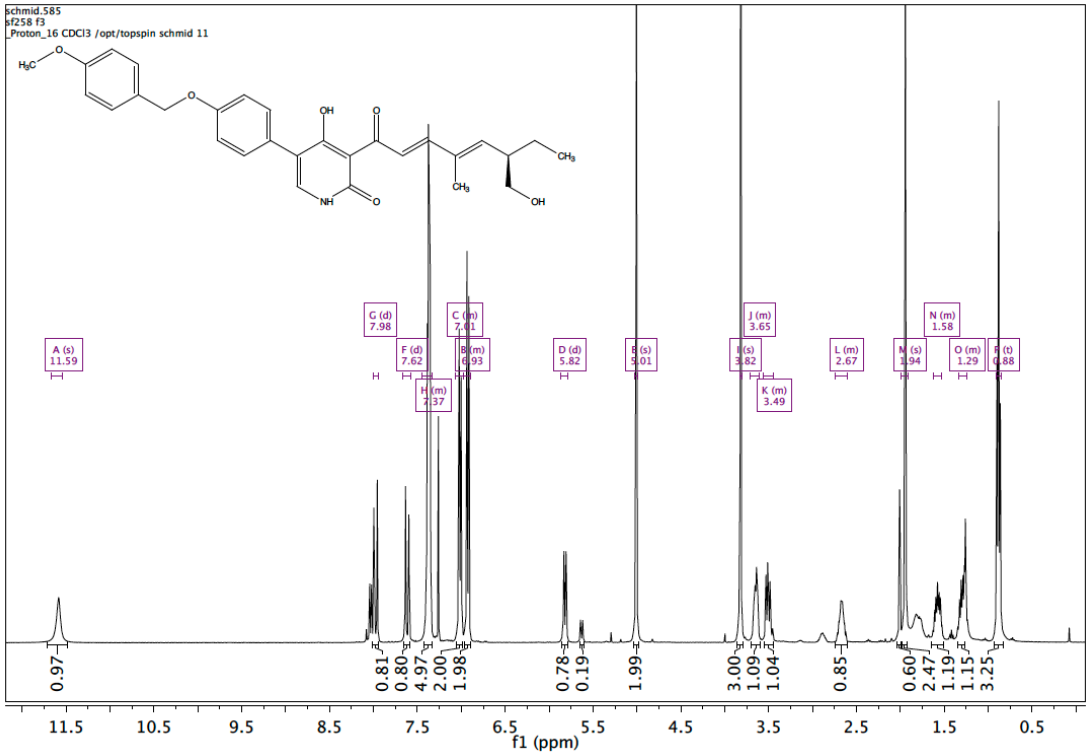
**3-((*R*,2*E*,4*E*)-6-(hydroxymethyl)-4-methylocta-2,4-dienoyl)-4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)pyridin-2(1H)-one (S5):**



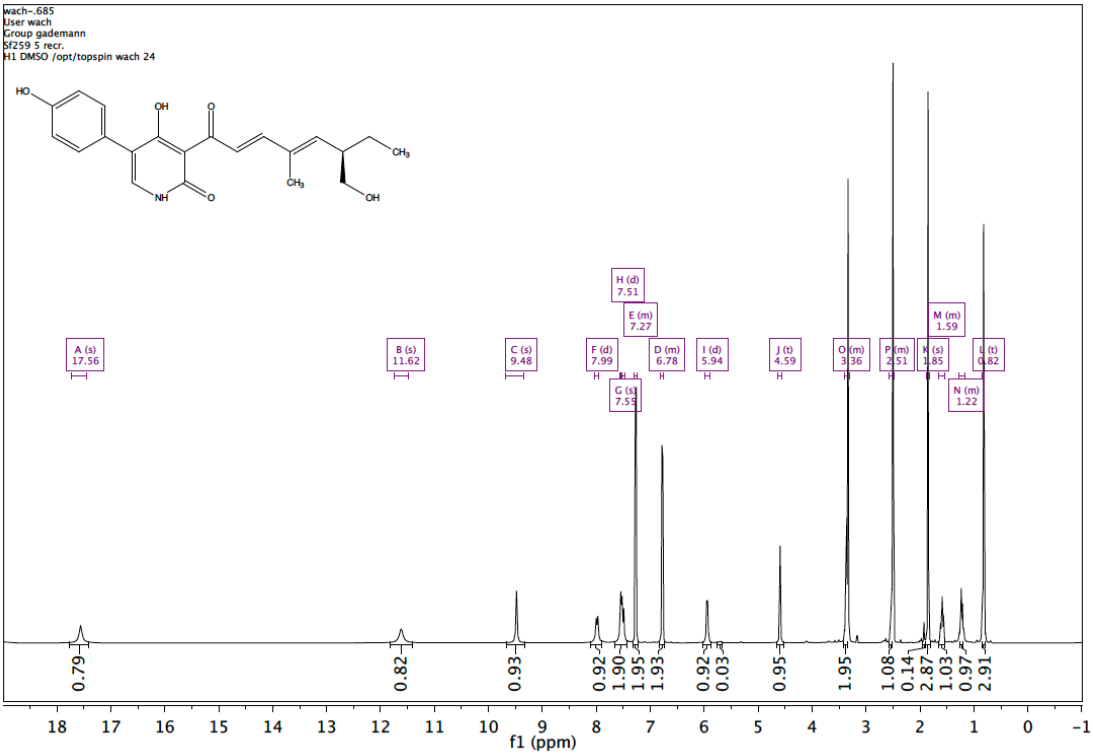



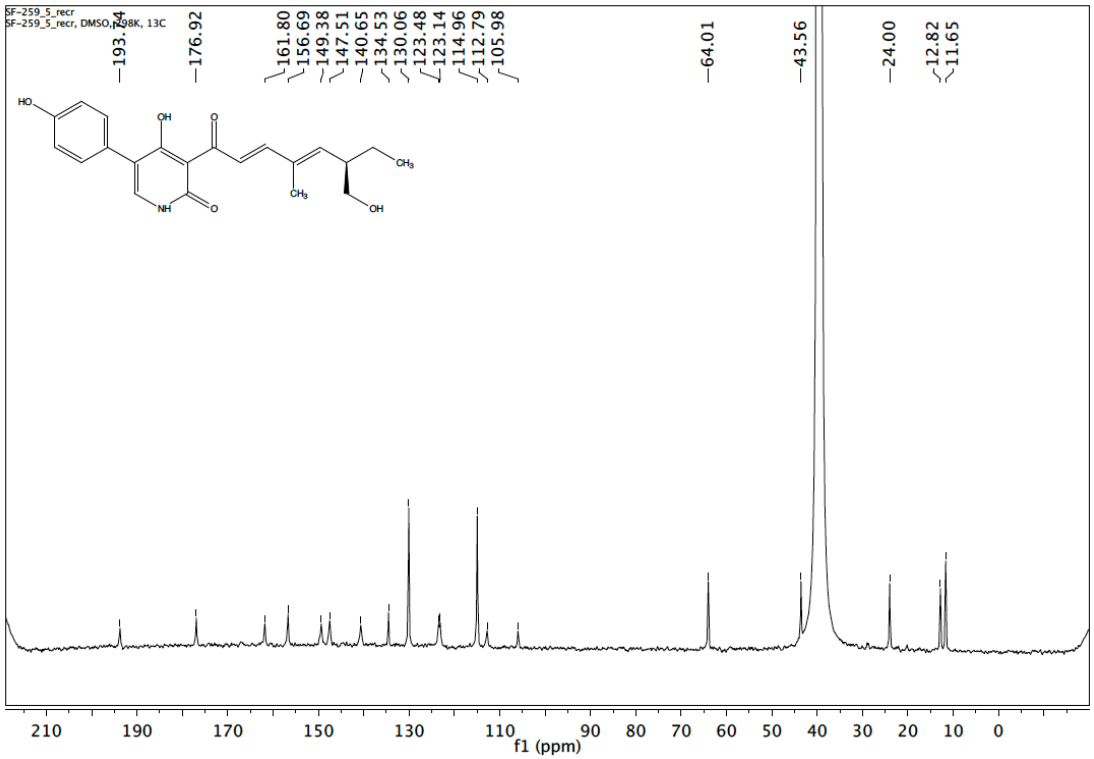

wach-.648
User wach
Group gademann
SF-254
_HMQC_GPSW CDCl3 /opt/topspin wach 43
{0.87,11.59}
{1.28,24.18}
{1.57,24.24}
{2.63,43.68}
{3.83,55.22}
{3.62,60.69}
{3.49,65.80}
{3.63,65.83}
{5.01,69.77}
{6.94,113.98}
{6.99,114.83}
{6.53,126.88}
{6.51,126.90}
{7.37,135.15}
{5.75,145.14}
{5.73,145.16}
{7.22,150.62}
{7.25,150.64}
f2 (ppm)
f1 (ppm)


wach-.648
User wach
Group gademann
SF-254
_HMBC_GPSW CDCl3 /opt/topspin wach 43
{7.00,126.39}
{5.01,130.31}
{1.89,135.97}
{7.38,129.43}
{5.01,129.40}
{7.30,158.64}
{5.01,158.65}
{3.62,165.56}
{7.38,159.65}
{7.00,158.65}
{3.61,168.35}
f2 (ppm)
f1 (ppm)

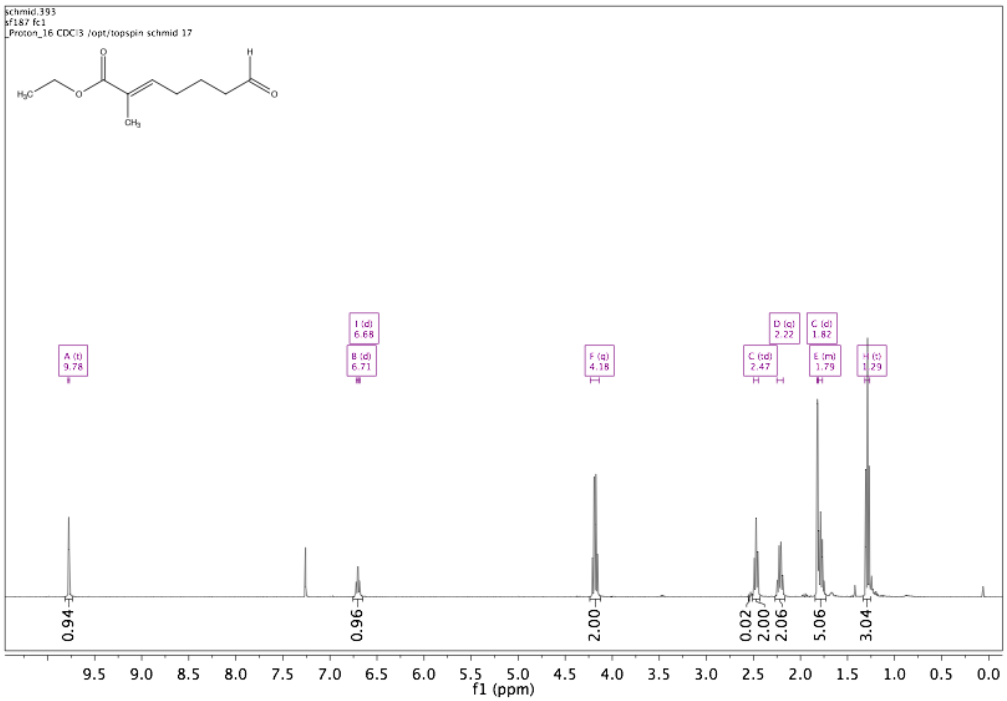

schmid.585
sf258 f3
_Proton_16 CDCl3 /opt/topspin schmid 11
A (s) 11.59
G (d) 7.98
F (d) 7.62
C (m) 7.41
B (m) 6.93
H (m) 2.37
D (d) 5.82
E (s) 5.01
J (m) 3.65
I (s) 3.82
K (m) 3.49
L (m) 2.67
M (s) 1.94
N (m) 1.58
O (m) 1.29
P (t) 0.88
0.97
0.81
0.80
4.97
2.00
1.98
0.78
0.19
1.99
3.00
1.09
1.04
0.85
0.60
2.47
1.19
1.15
3.25
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

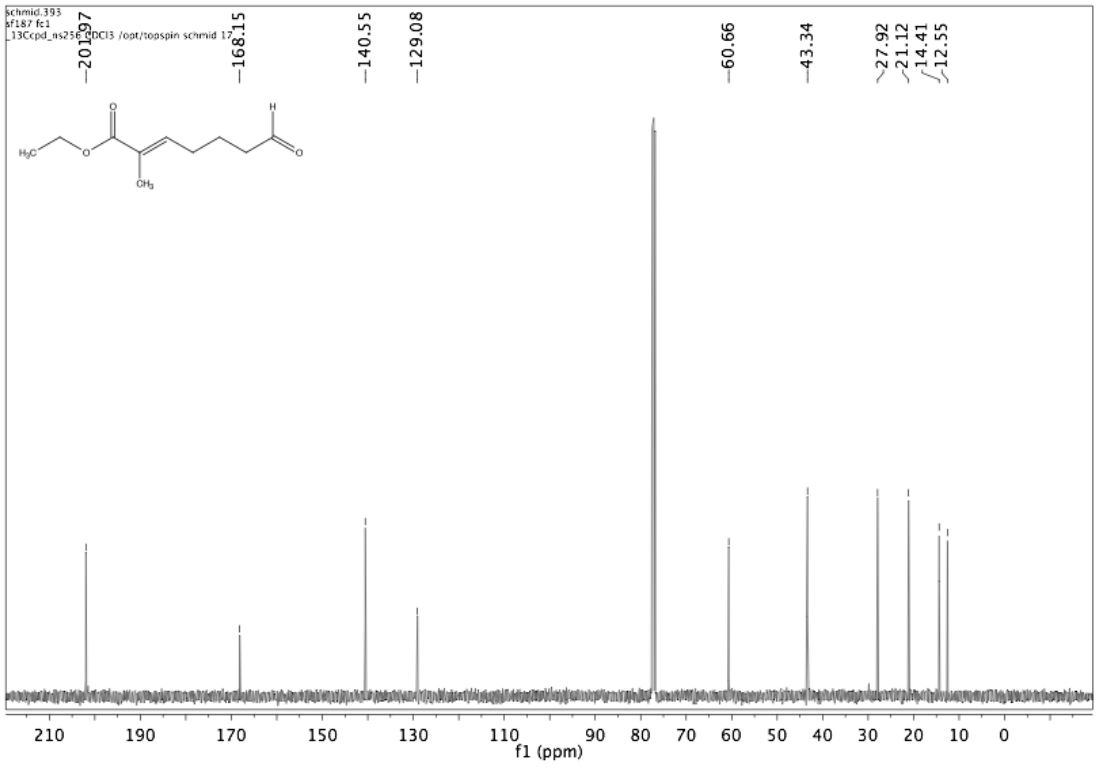
## (–)-Pyridovericin (2.46):



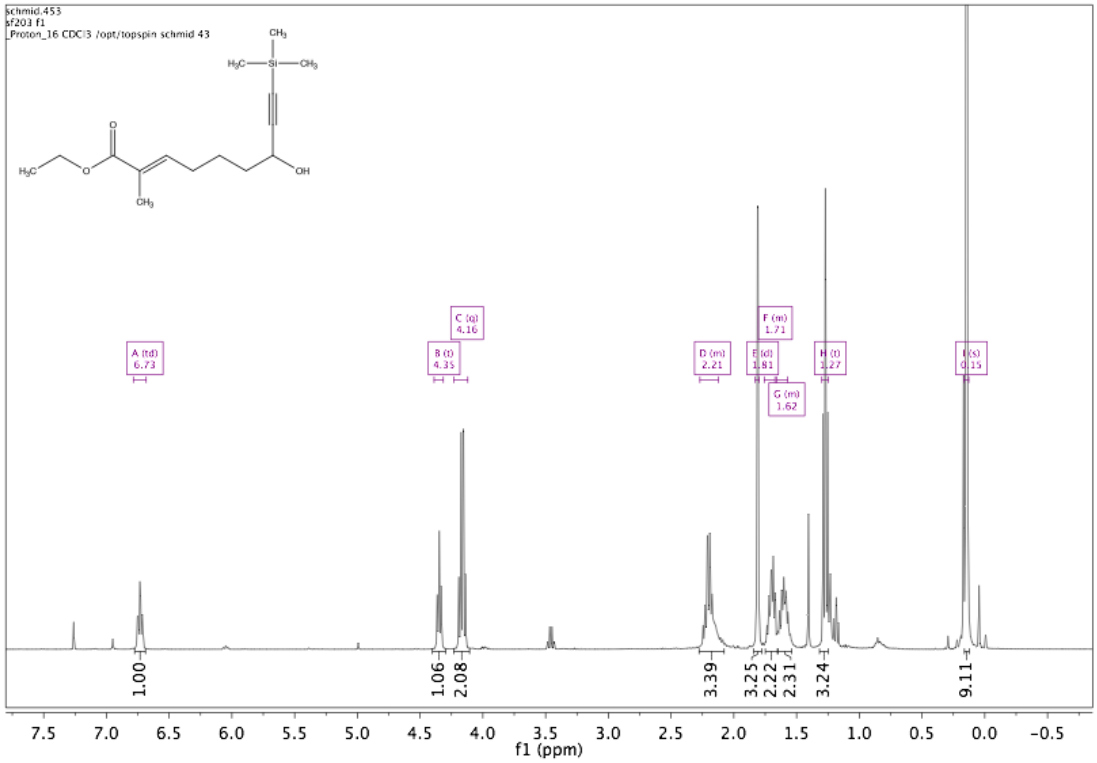
**(*E*)-ethyl 2-methyl-7-oxohept-2-enoate (3.31):**[321]

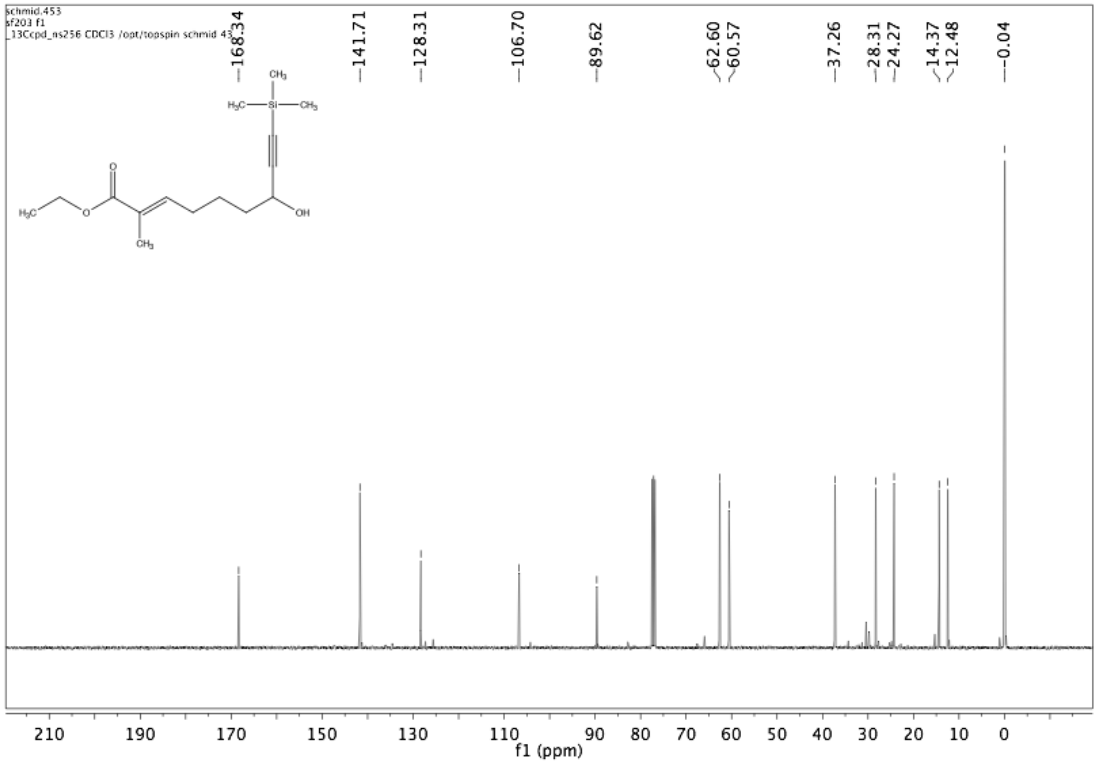


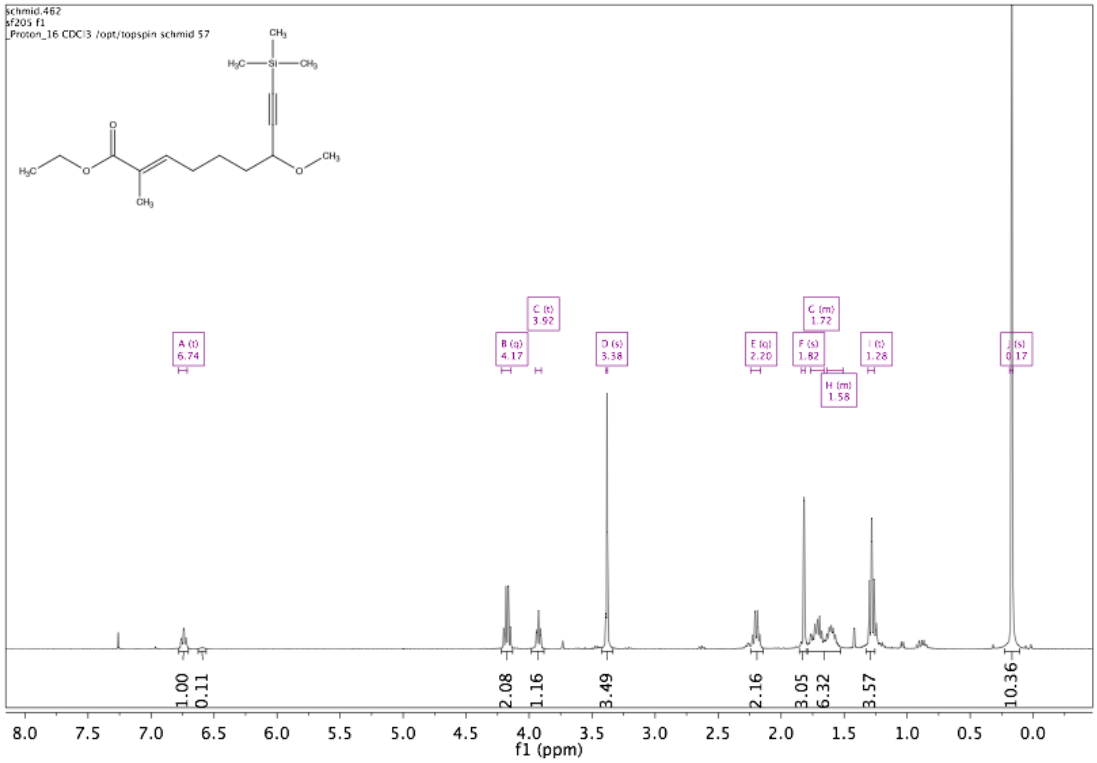

[321] E. L. Richards, P. J. Murphy, F. Dinon, S. Fratucello, P. M. Brown, T. Gelbrich, Michael B. Hursthouse, *Tetrahedron* **2001**, *57*, 7771.

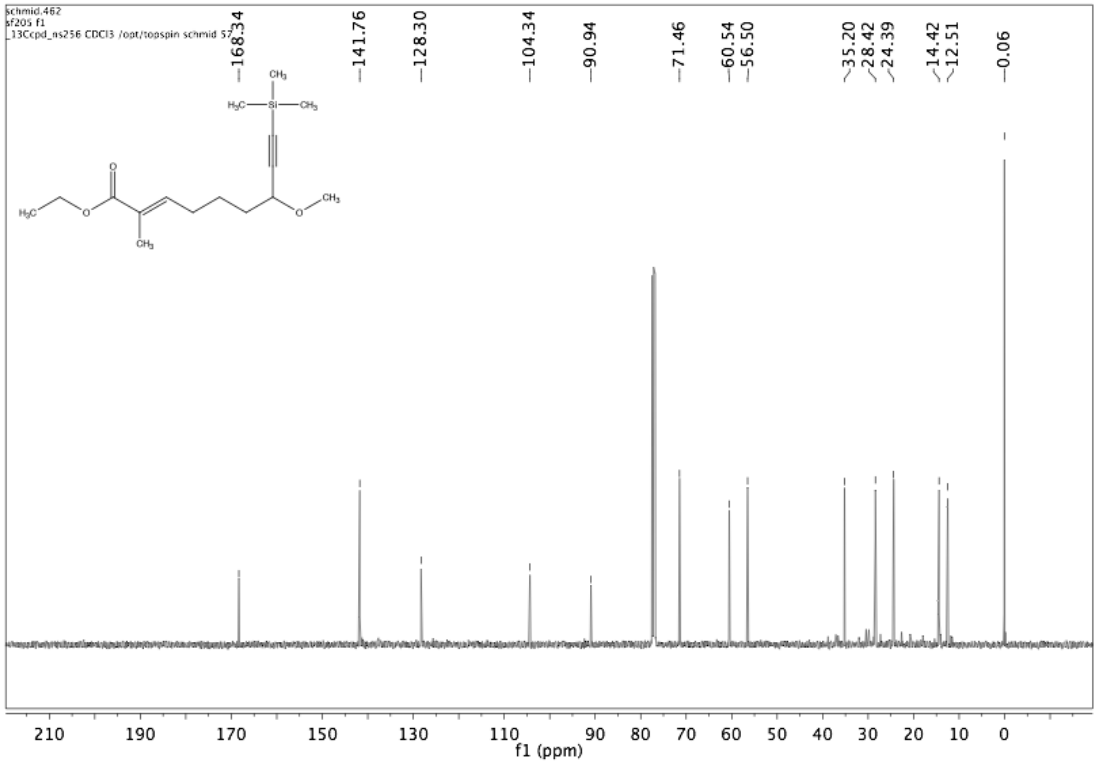
**(*E*)-ethyl 7-hydroxy-2-methyl-9-(trimethylsilyl)non-2-en-8-ynoate (S7):**



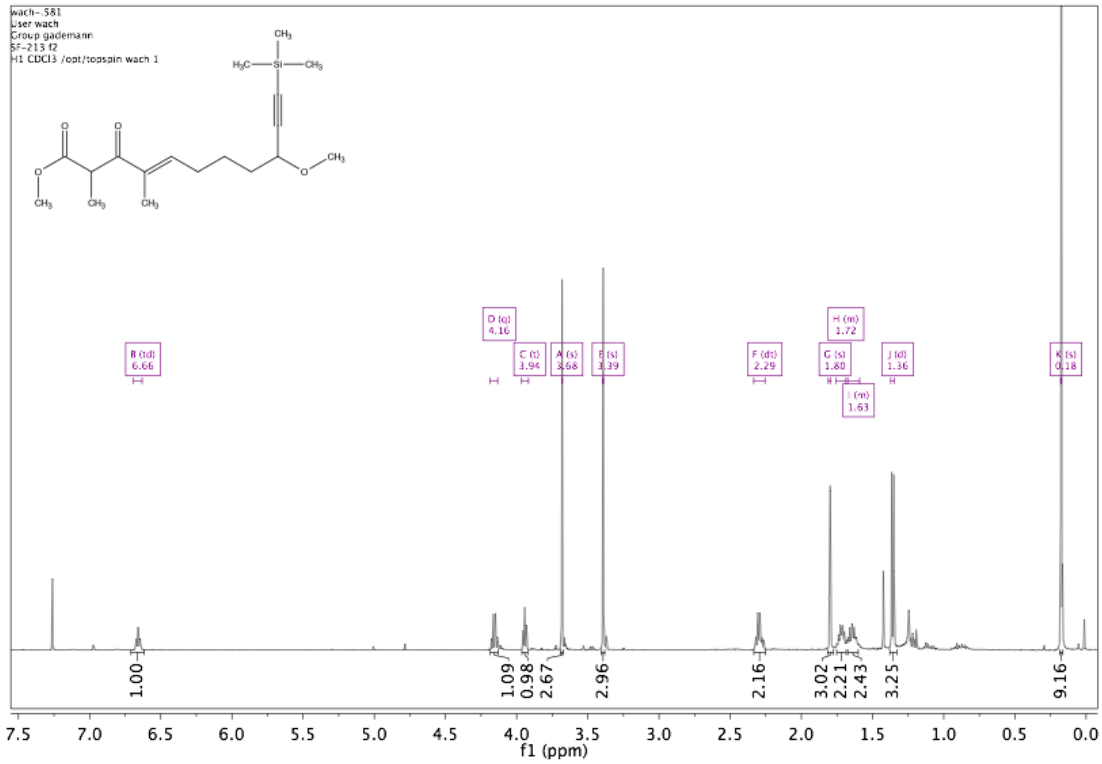



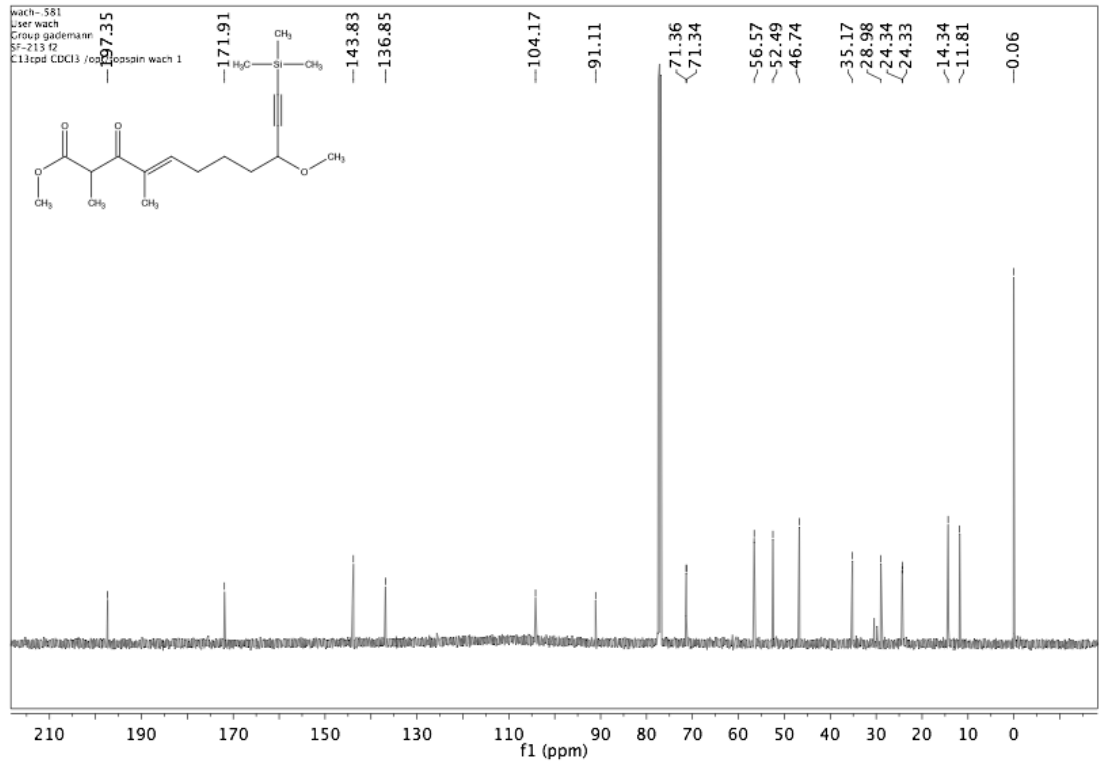
**(*E*)-ethyl 7-methoxy-2-methyl-9-(trimethylsilyl)non-2-en-8-ynoate (3.32):**



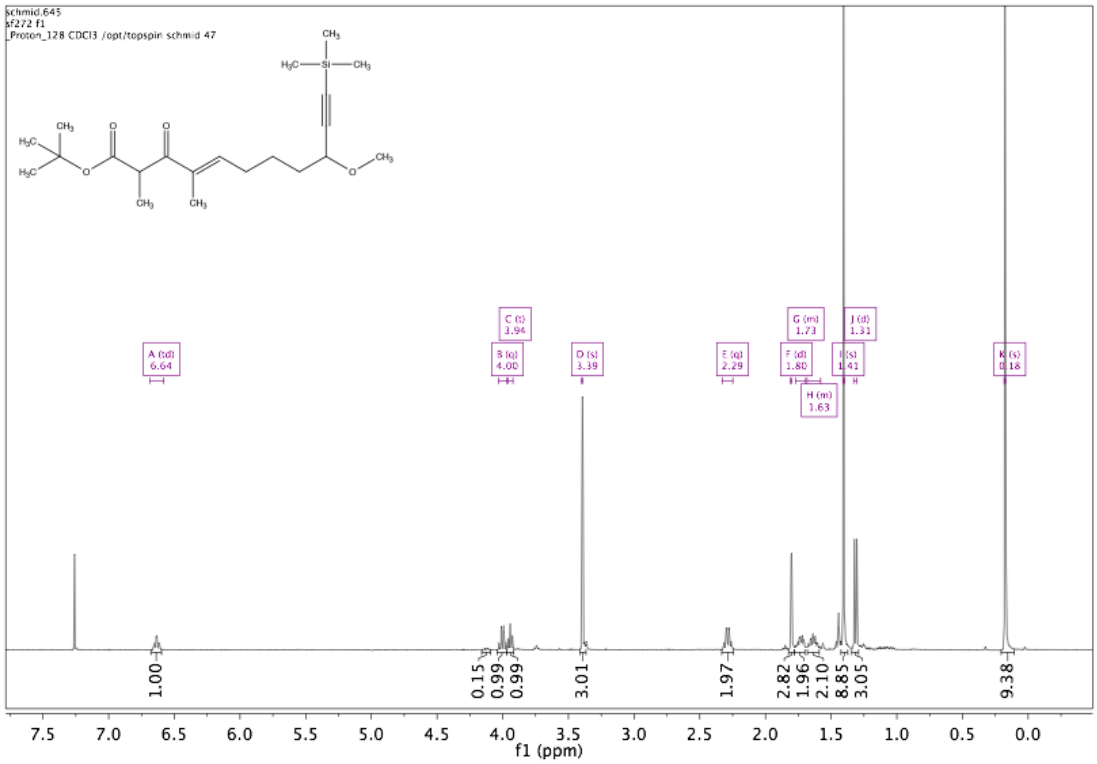



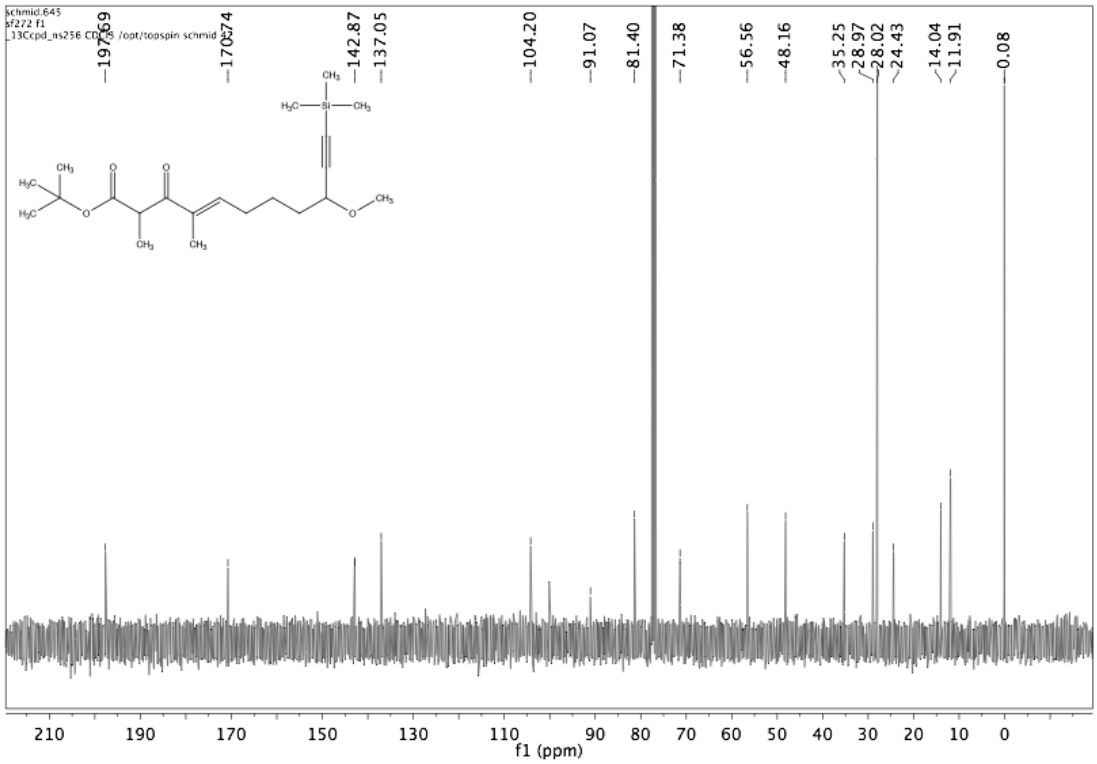
**(*E*)-methyl 9-methoxy-2,4-dimethyl-3-oxo-11-(trimethylsilyl)undec-4-en-10-ynoate (S8):**



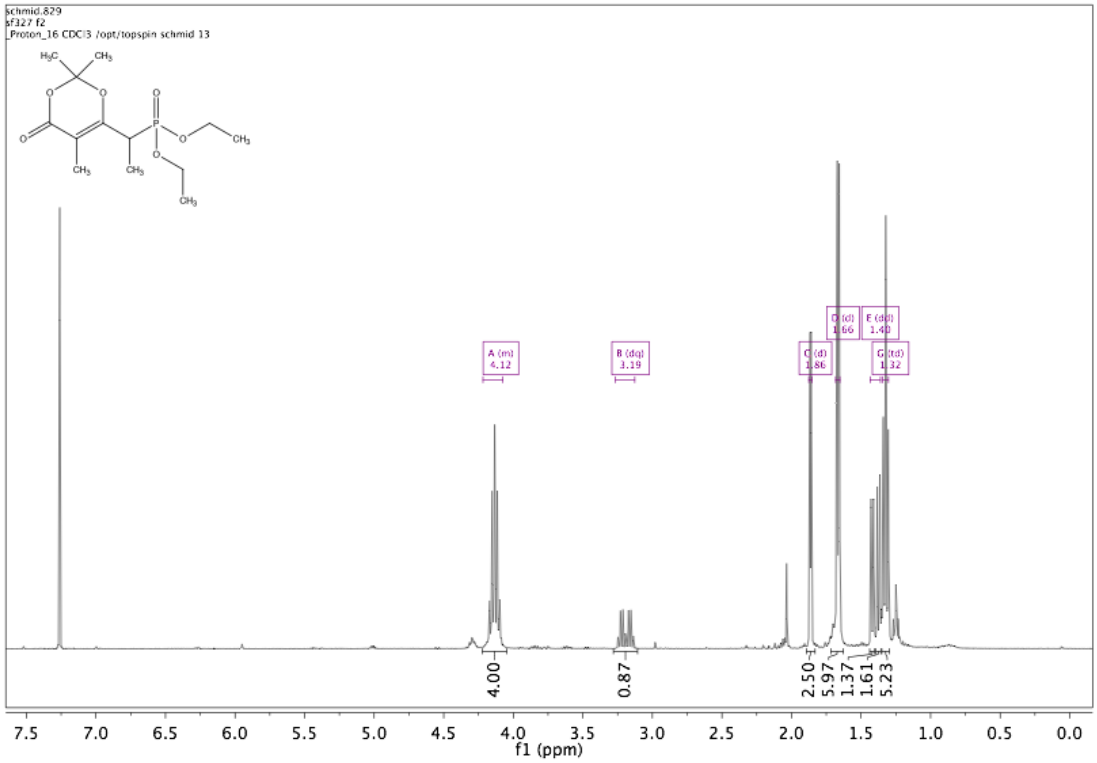



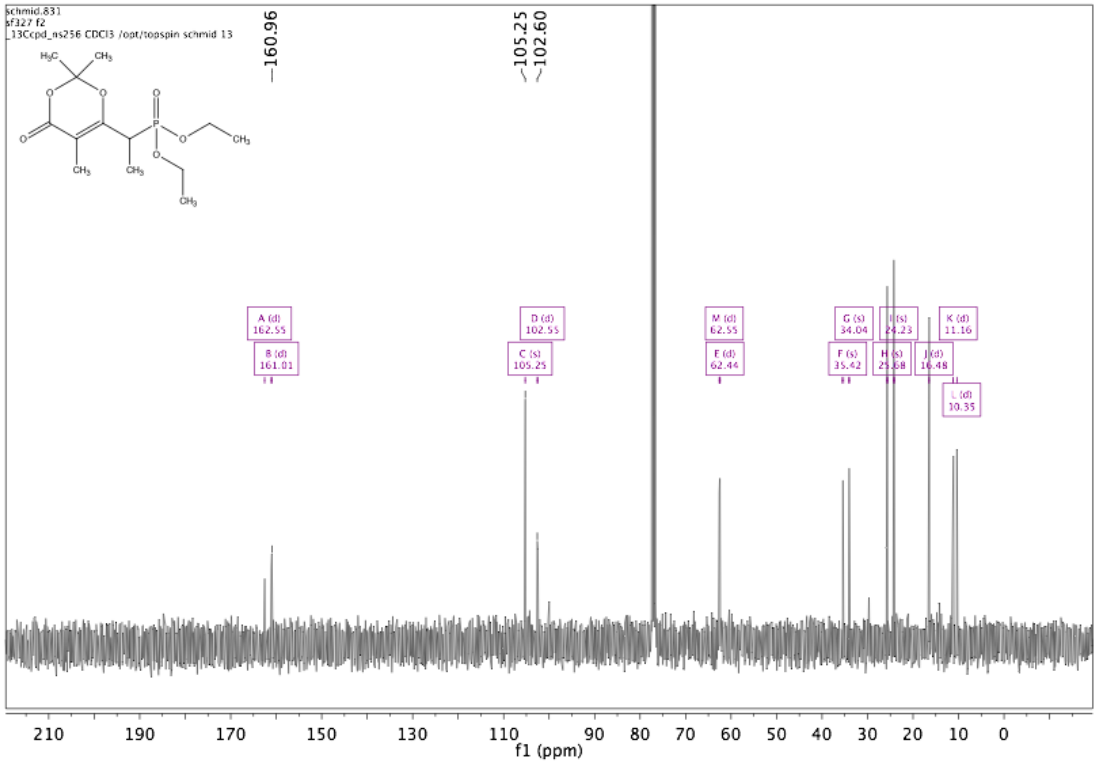
**(*E*)-*tert*-butyl 9-methoxy-2,4-dimethyl-3-oxo-11-(trimethylsilyl)undec-4-en-10-ynoate (S9):**



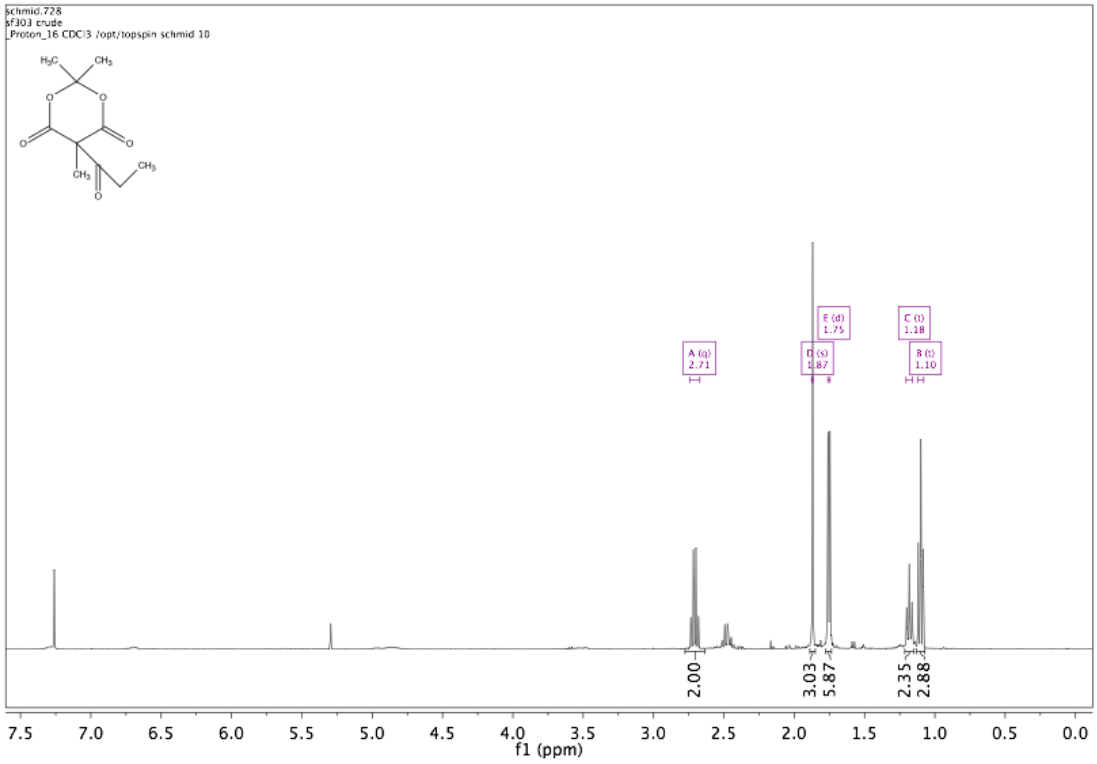



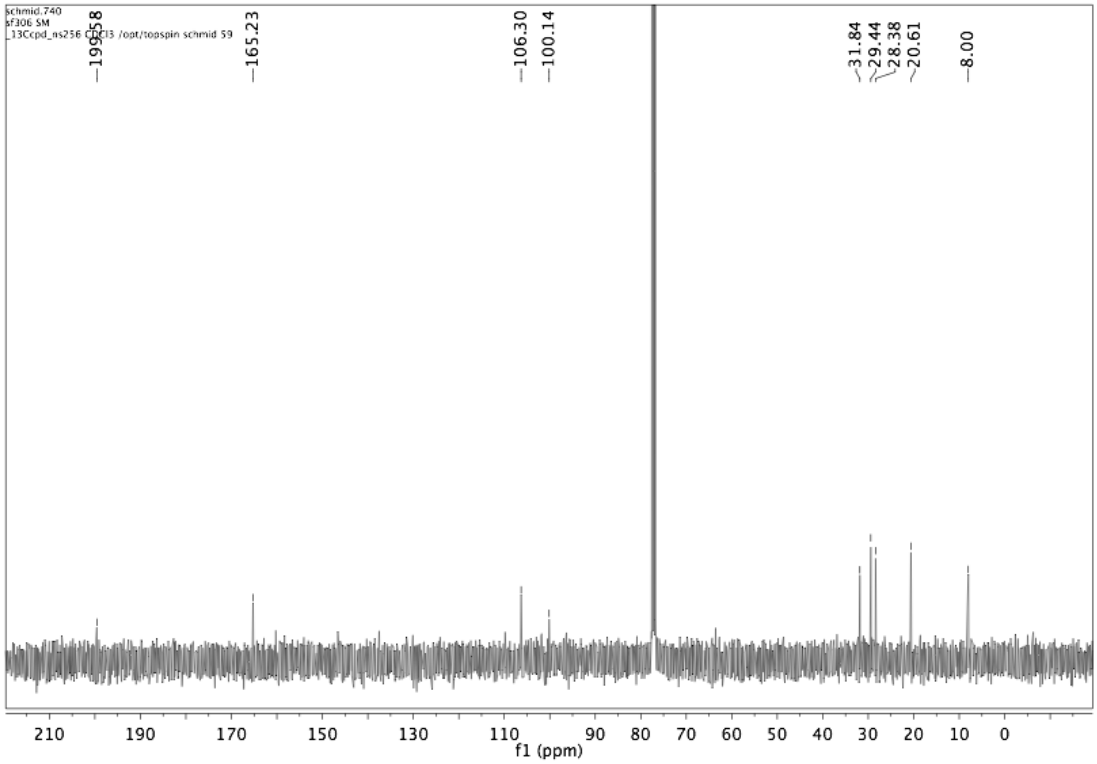
**Diethyl (1-(2,2,5-trimethyl-4-oxo-4H-1,3-dioxin-6-yl)ethyl)phosphonate (3.44):**



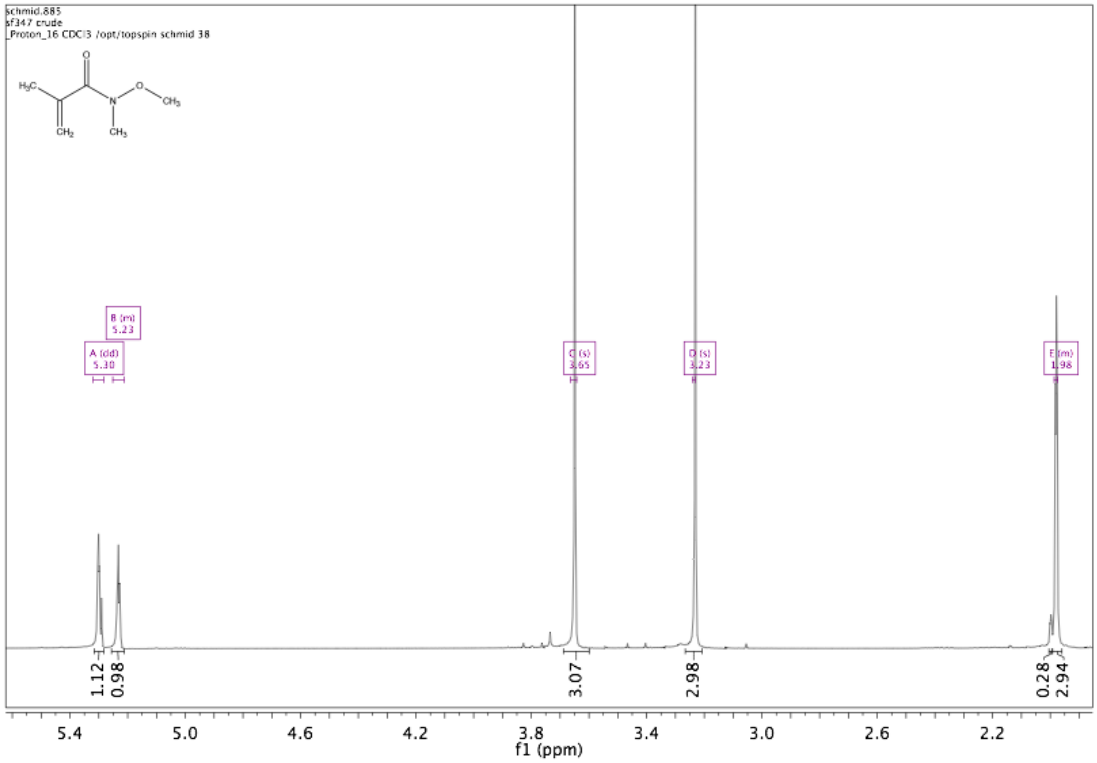



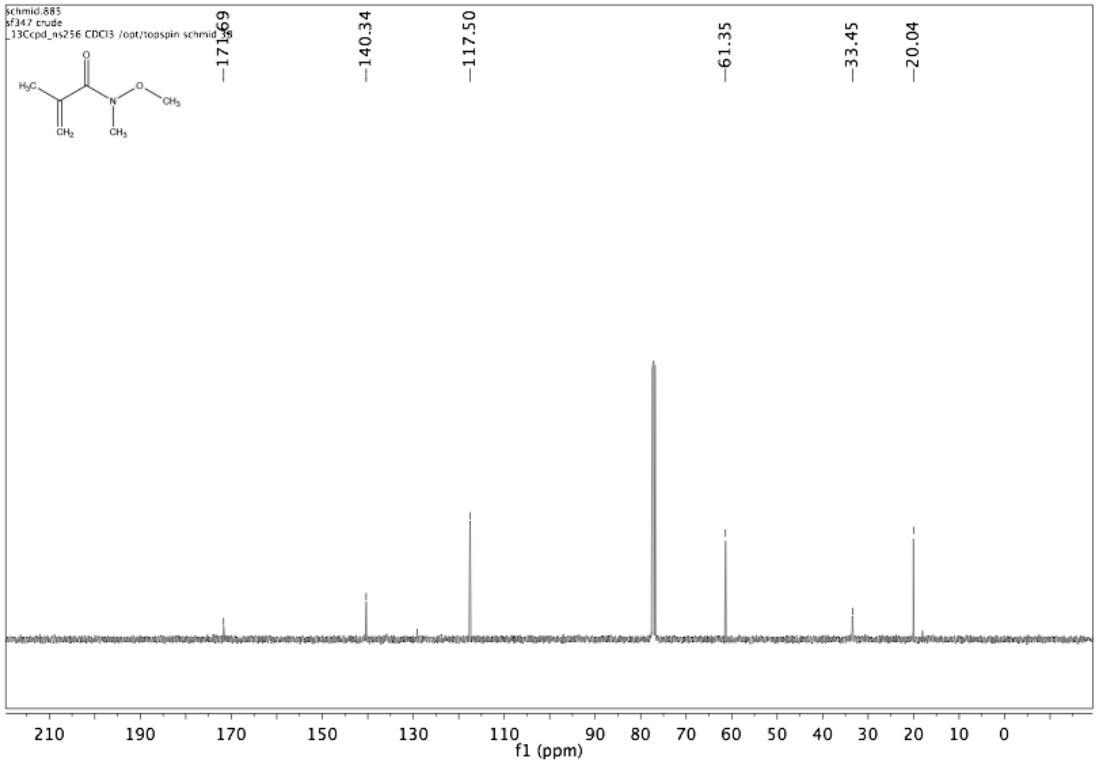
**2,2,5-Trimethyl-5-propionyl-1,3-dioxane-4,6-dione (S10):**



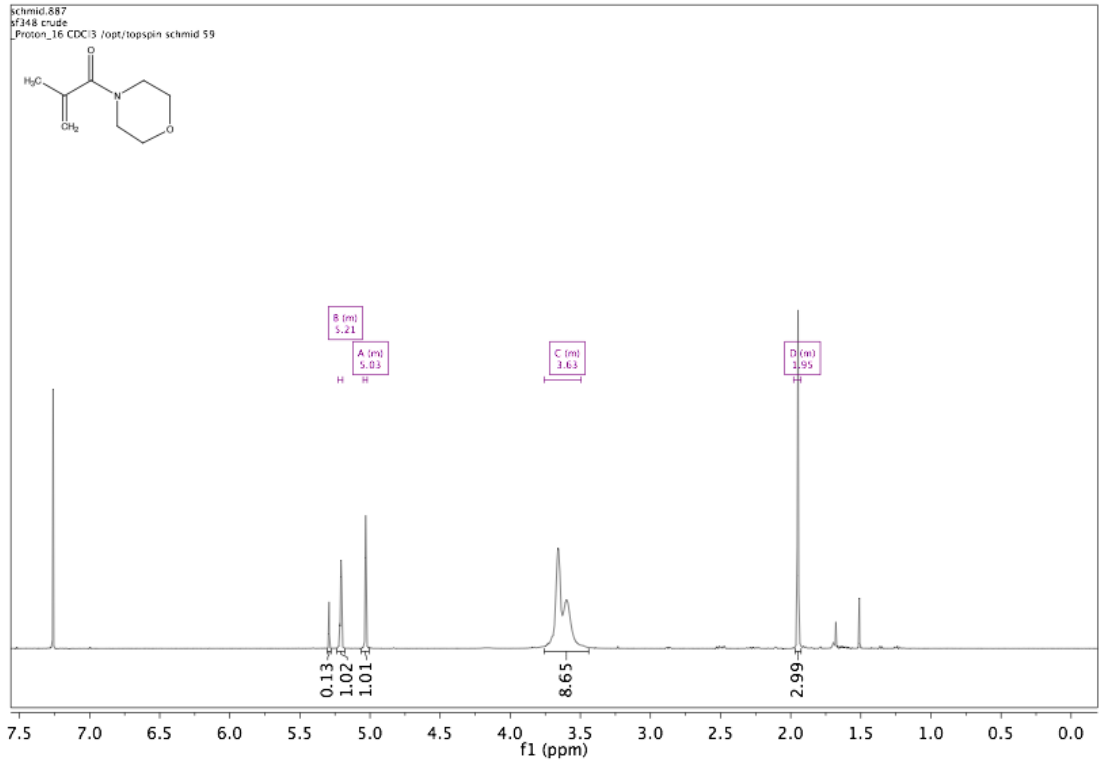



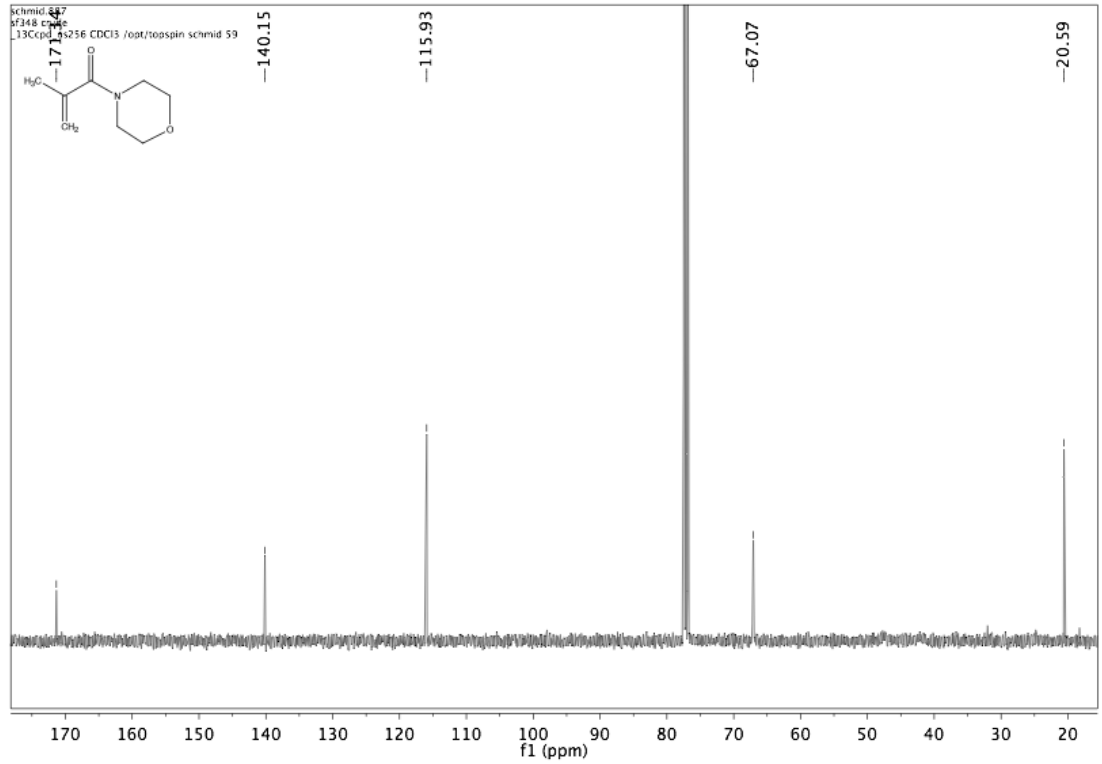
***N*-methoxy-*N*-methylmethacrylamide (S11):**



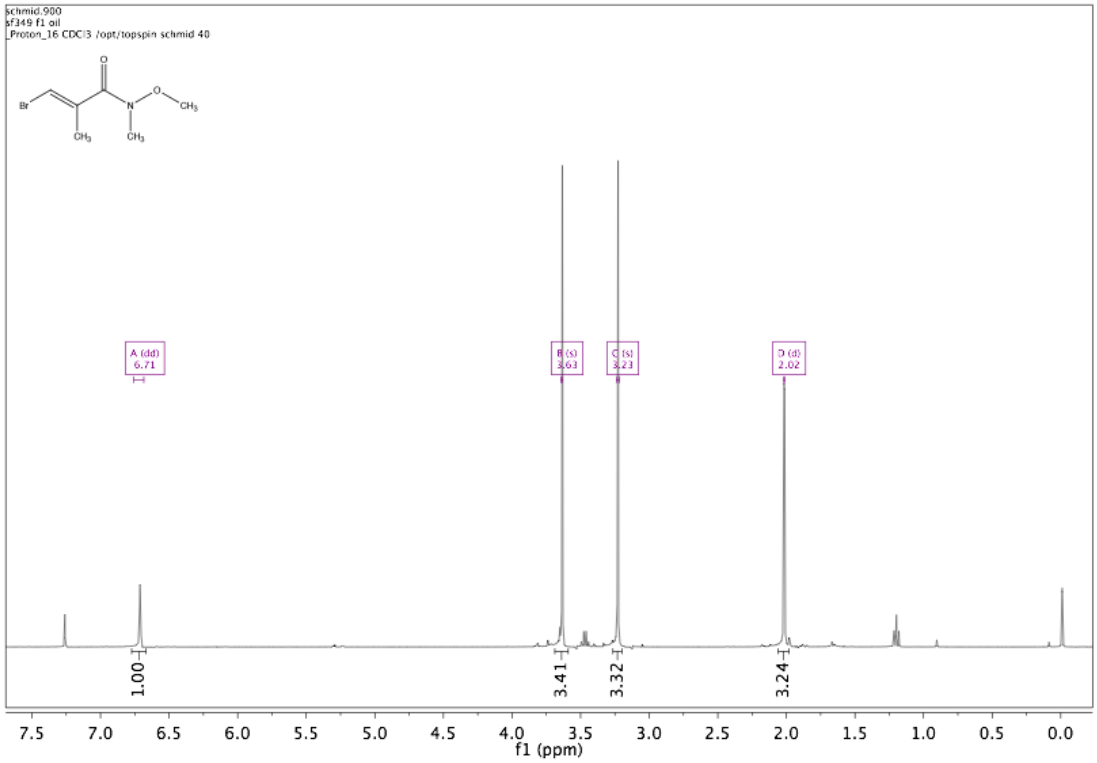



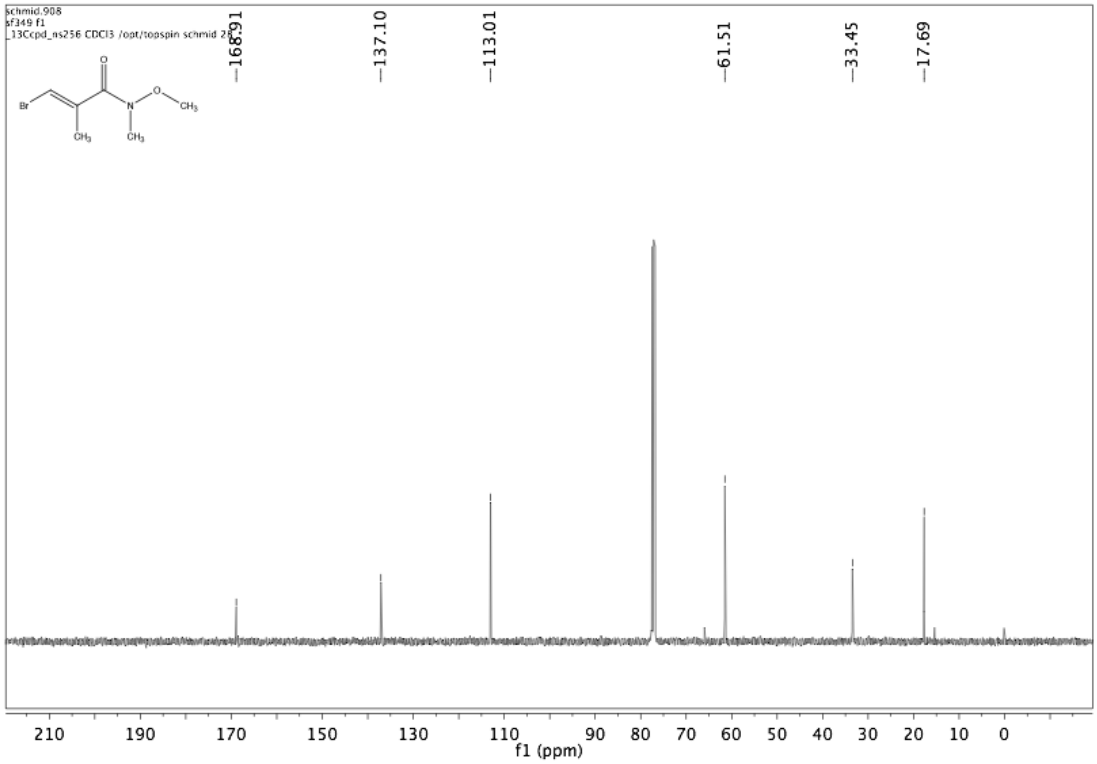
**2-Methyl-1-morpholinoprop-2-en-1-one (S12):**



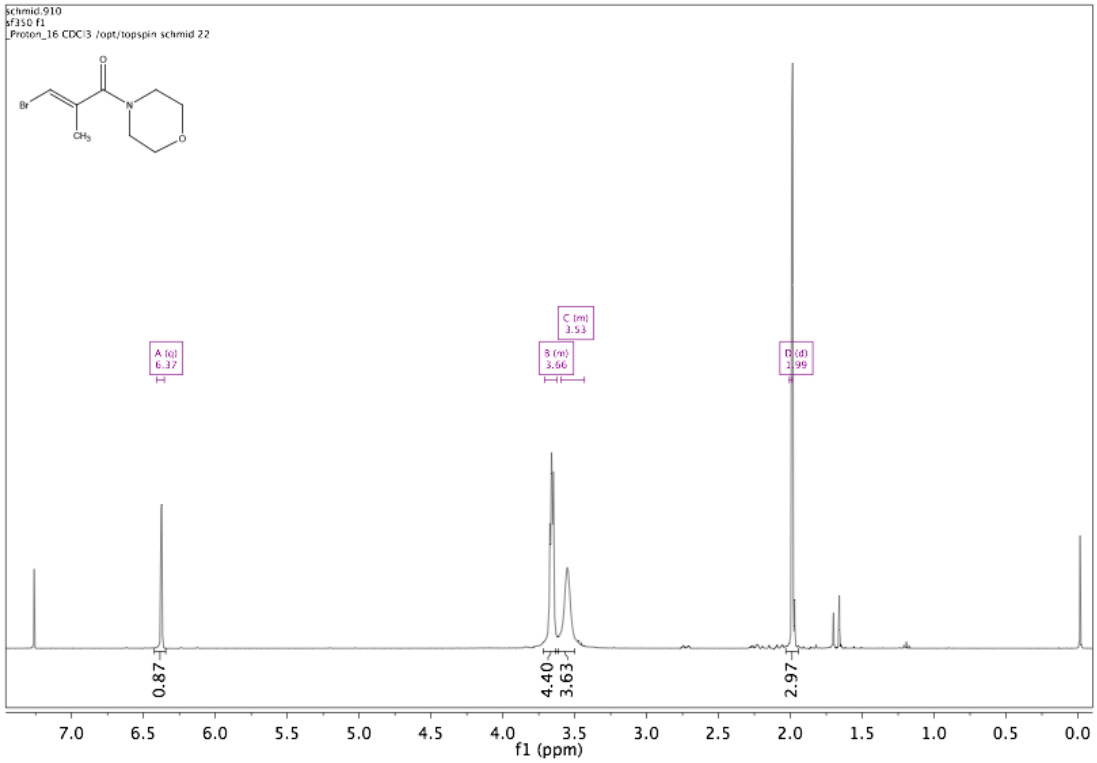



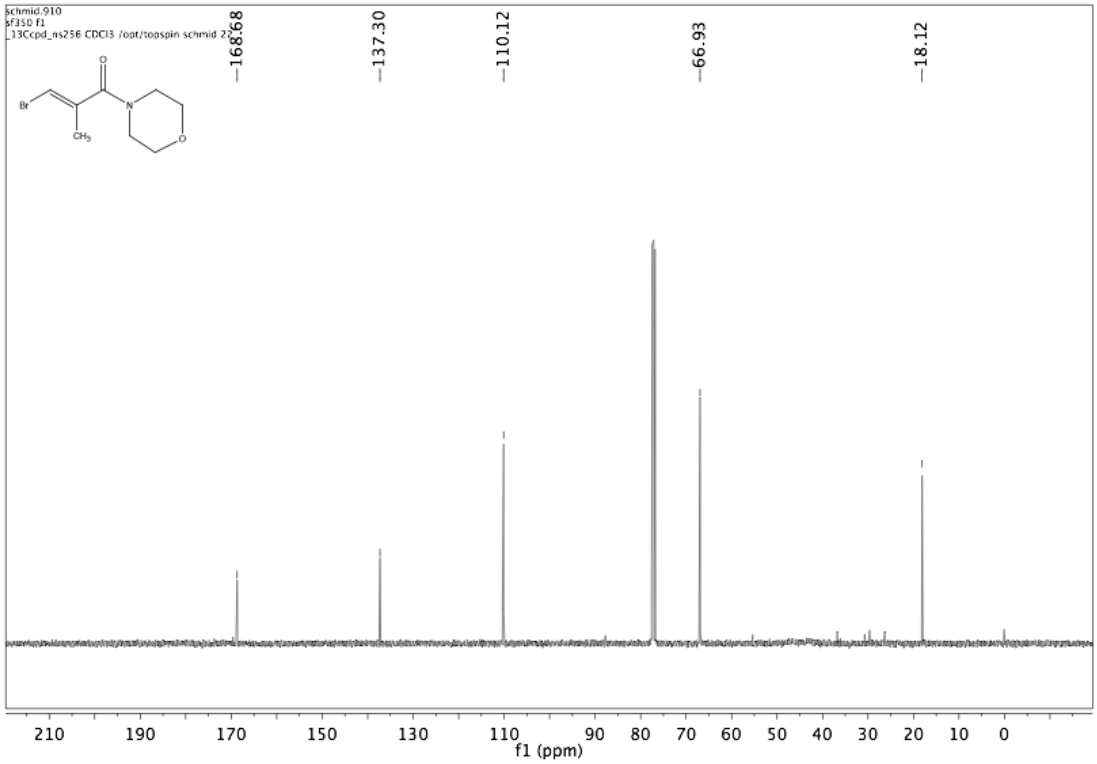
**(*E*)-3-bromo-*N*-methoxy-*N*,2-dimethylacrylamide (3.58):**



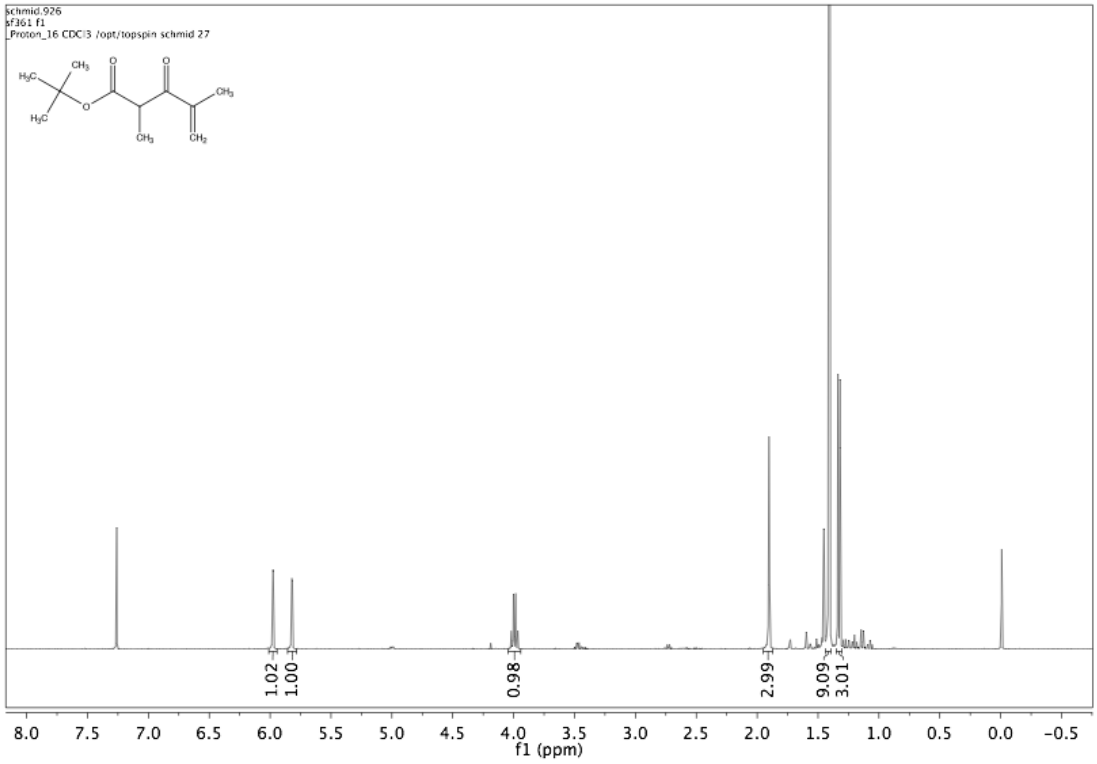



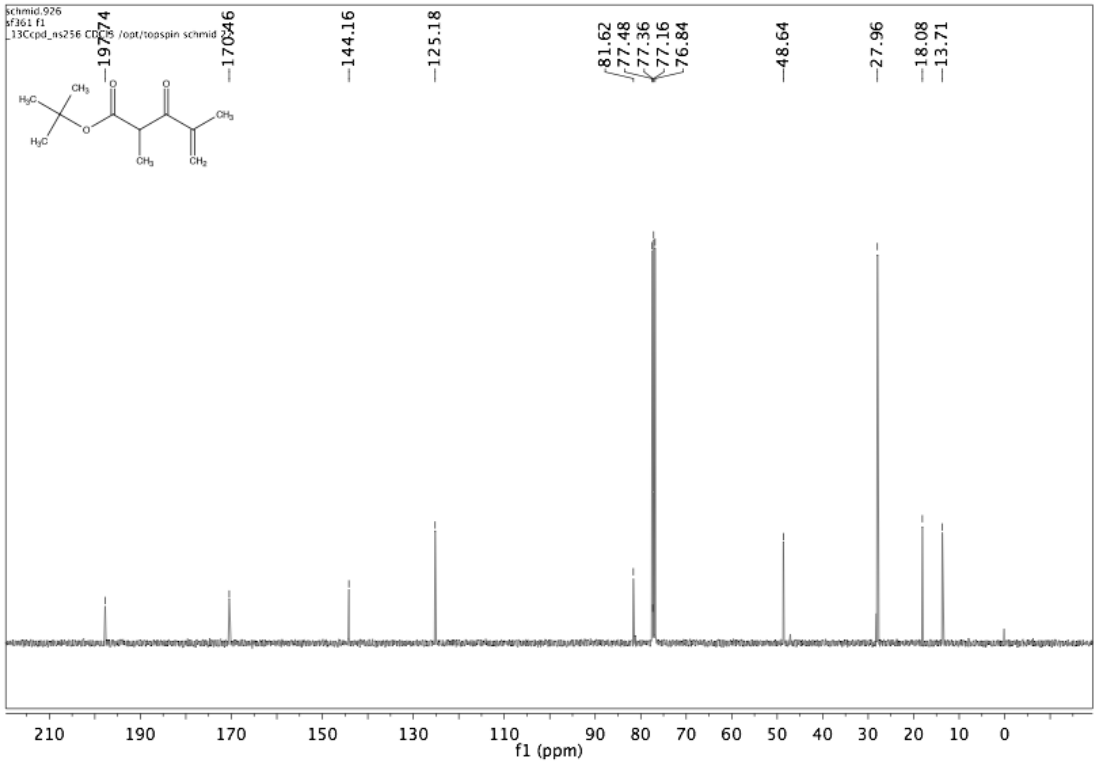
**(*E*)-3-bromo-2-methyl-1-morpholinoprop-2-en-1-one (3.59):**



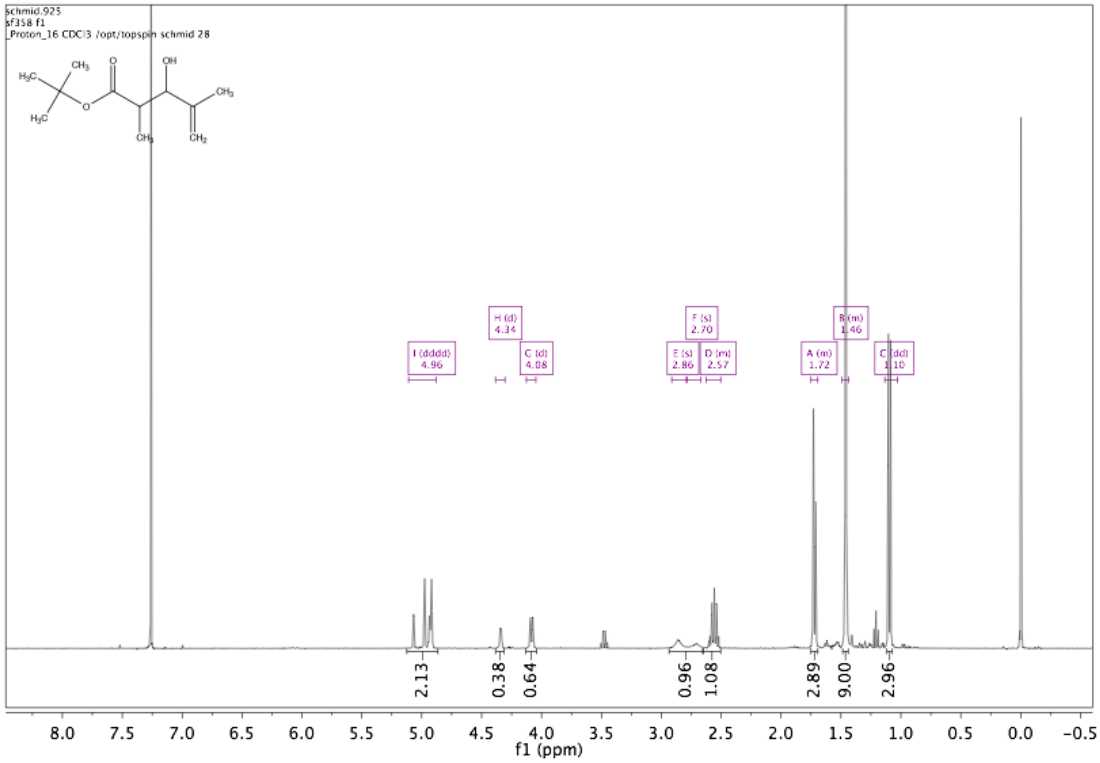



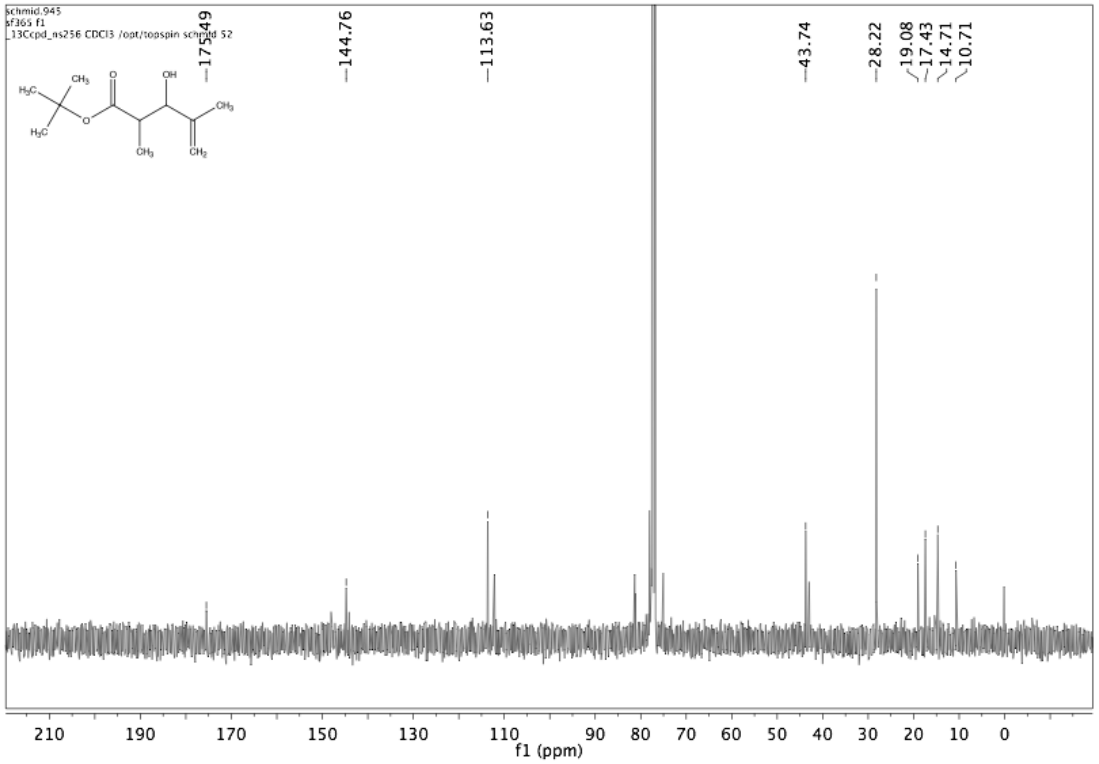
***tert*-butyl 2,4-dimethyl-3-oxopent-4-enoate (S42):**



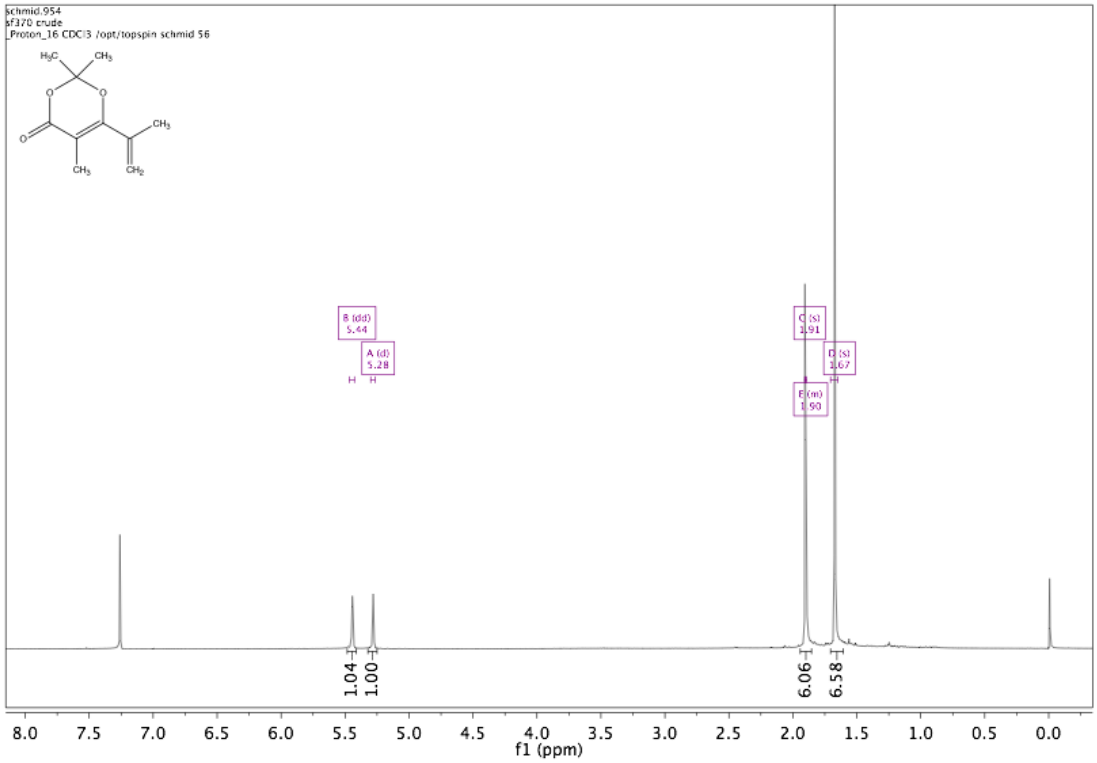



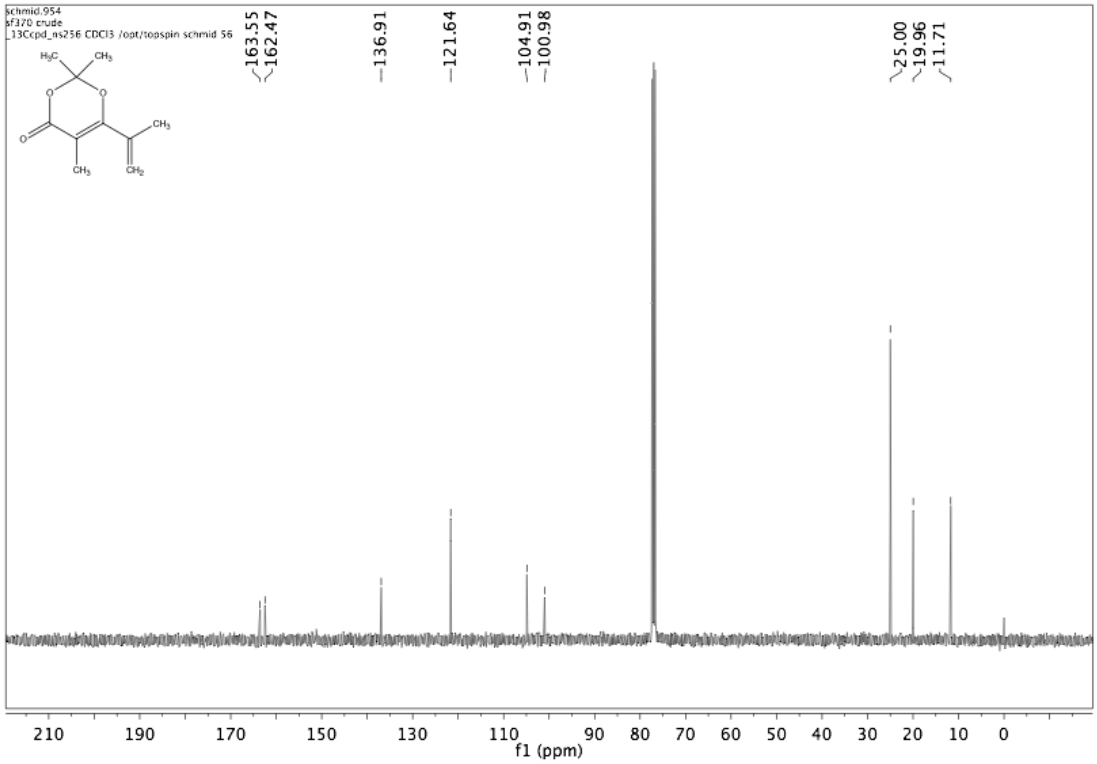
***tert*-Butyl 3-hydroxy-2,4-dimethylpent-4-enoate (S13):**



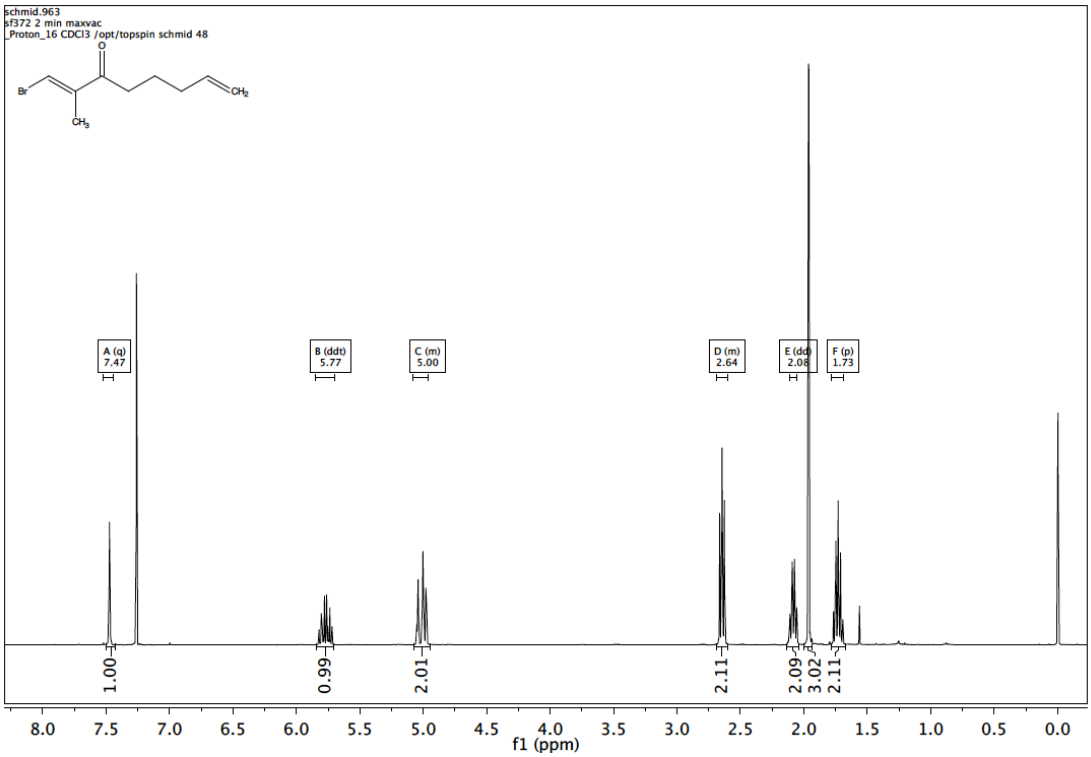



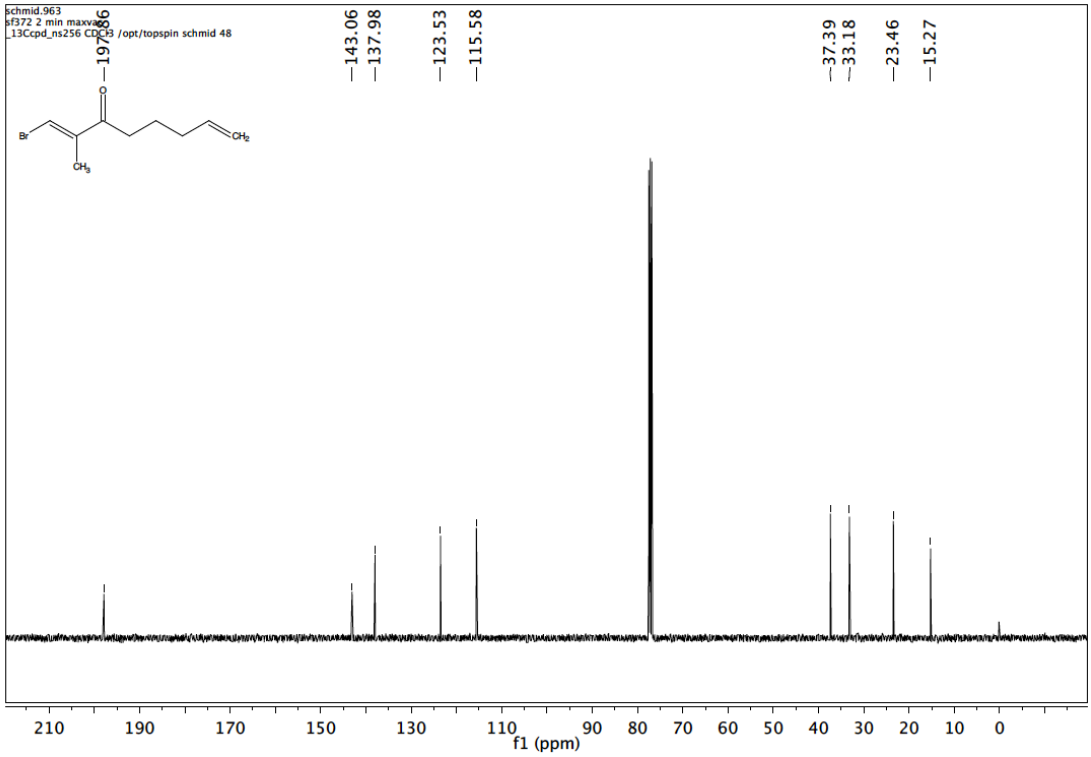
**2,2,5-trimethyl-6-(prop-1-en-2-yl)-4H-1,3-dioxin-4-one (3.52):**



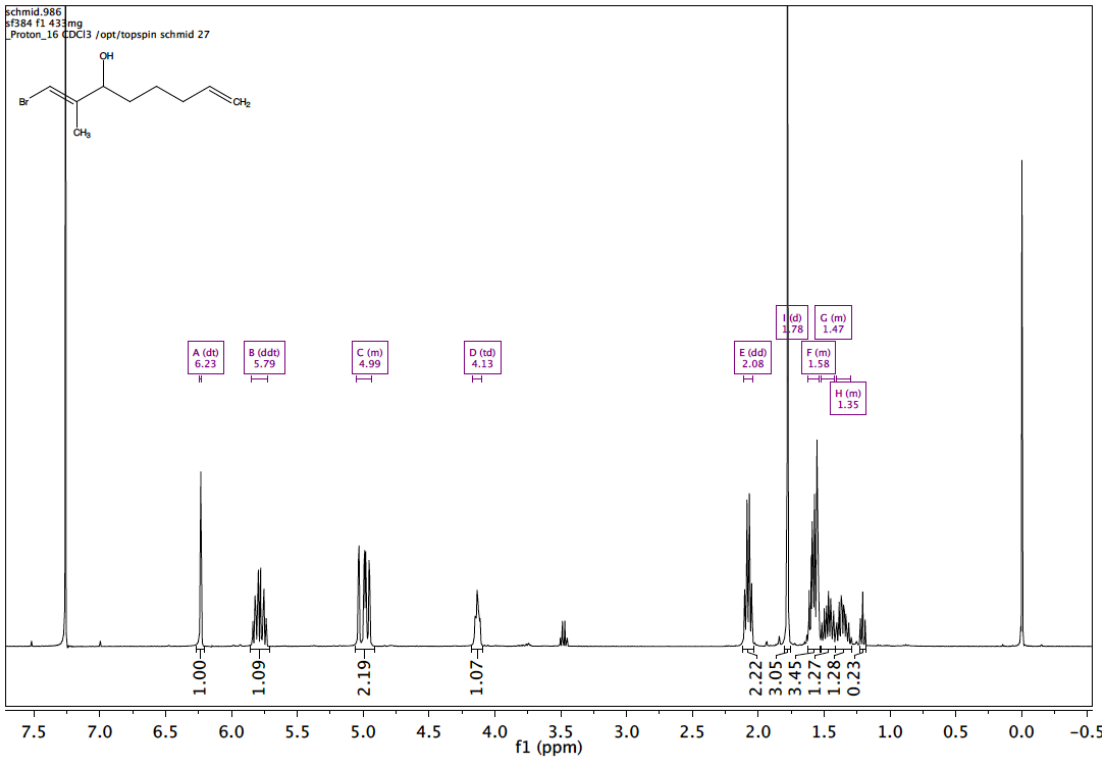



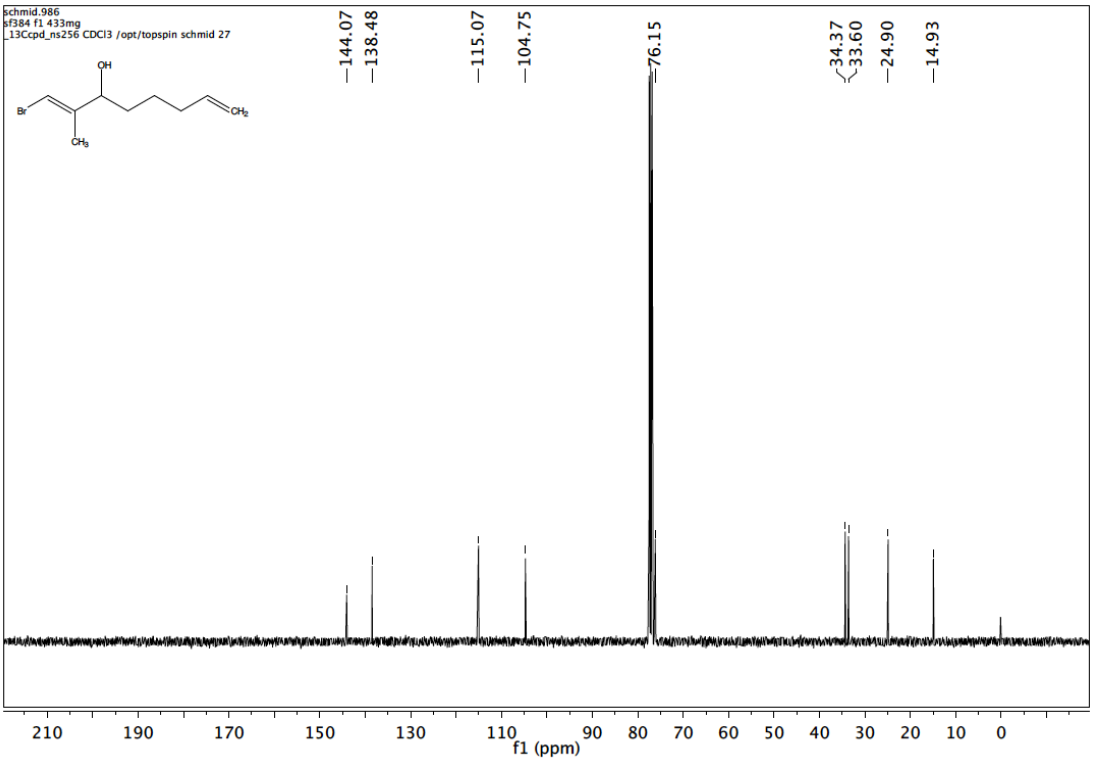
**(*E*)-1-bromo-2-methylocta-1,7-dien-3-one (3.60):**



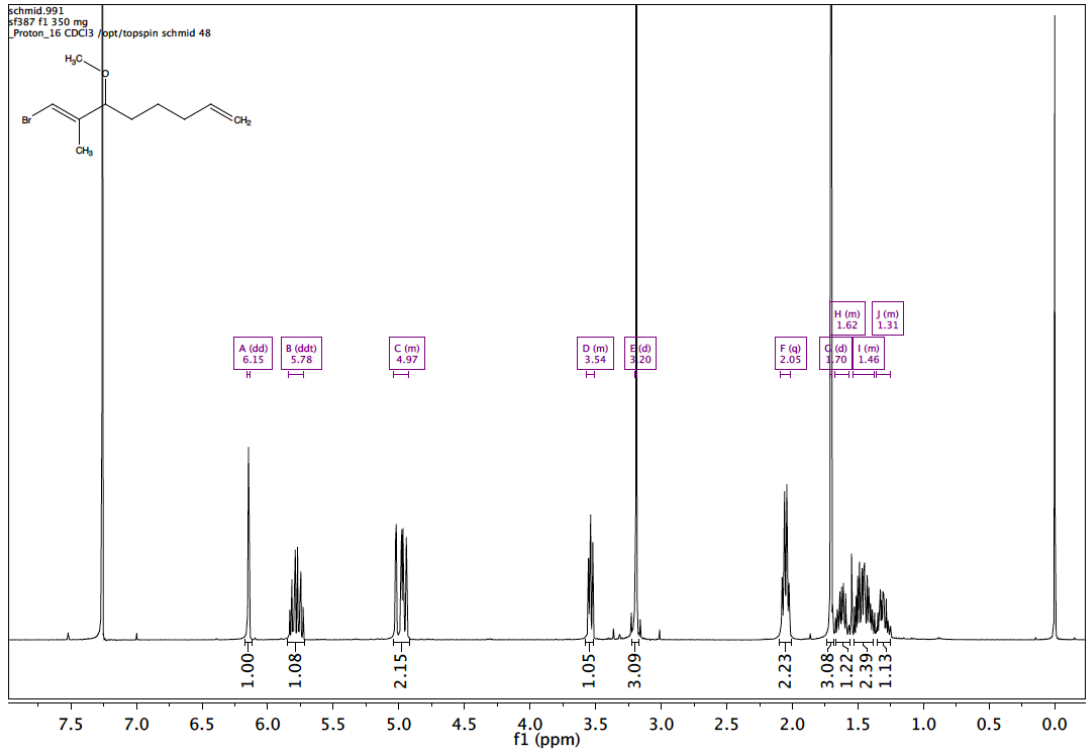



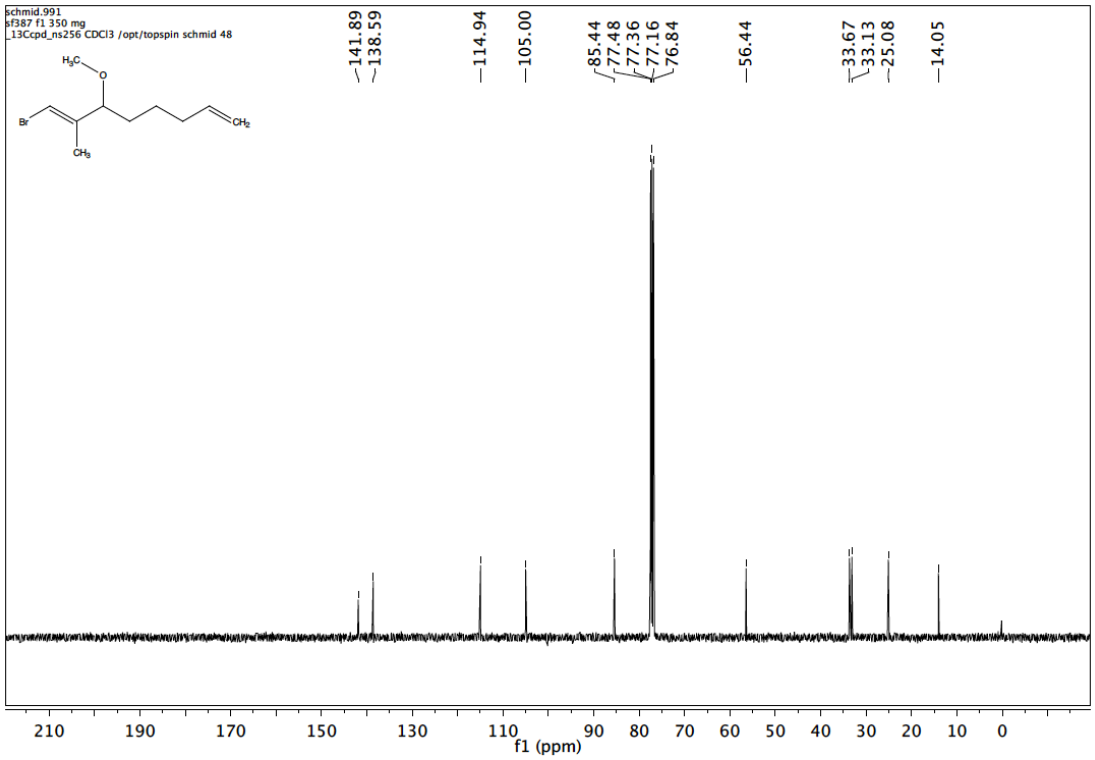
**(*E*)-1-bromo-2-methylocta-1,7-dien-3-ol (S14):**



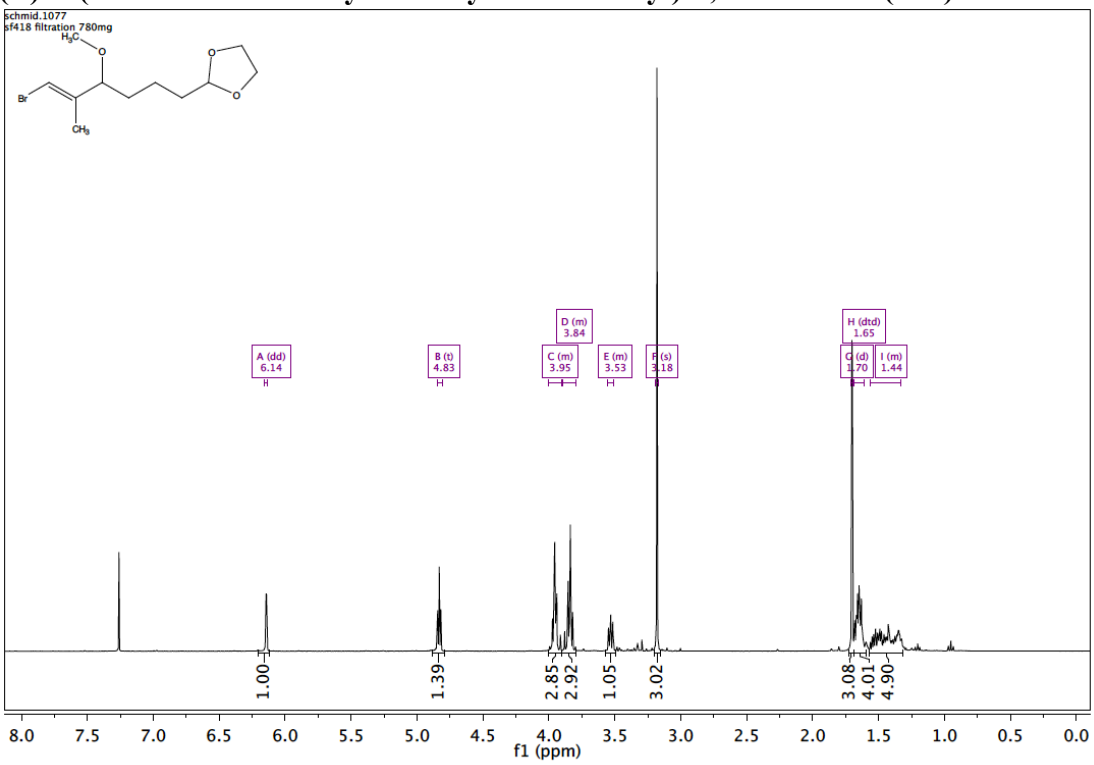



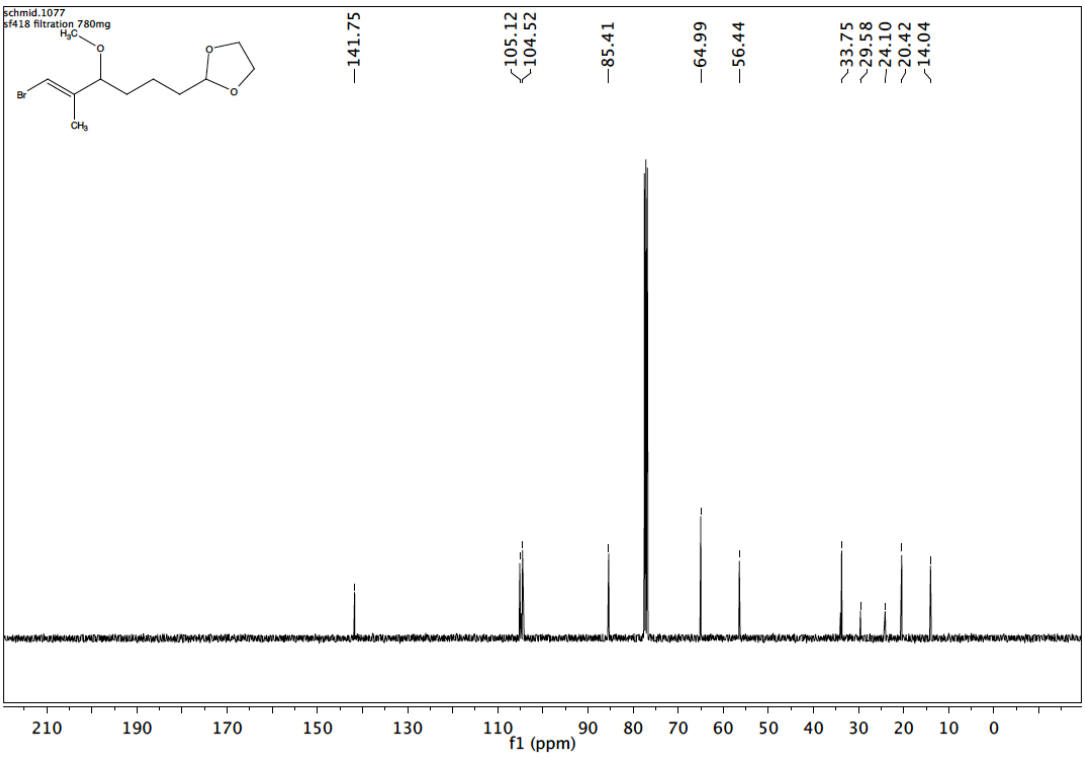
**(*E*)-1-bromo-3-methoxy-2-methylocta-1,7-diene (3.53):**



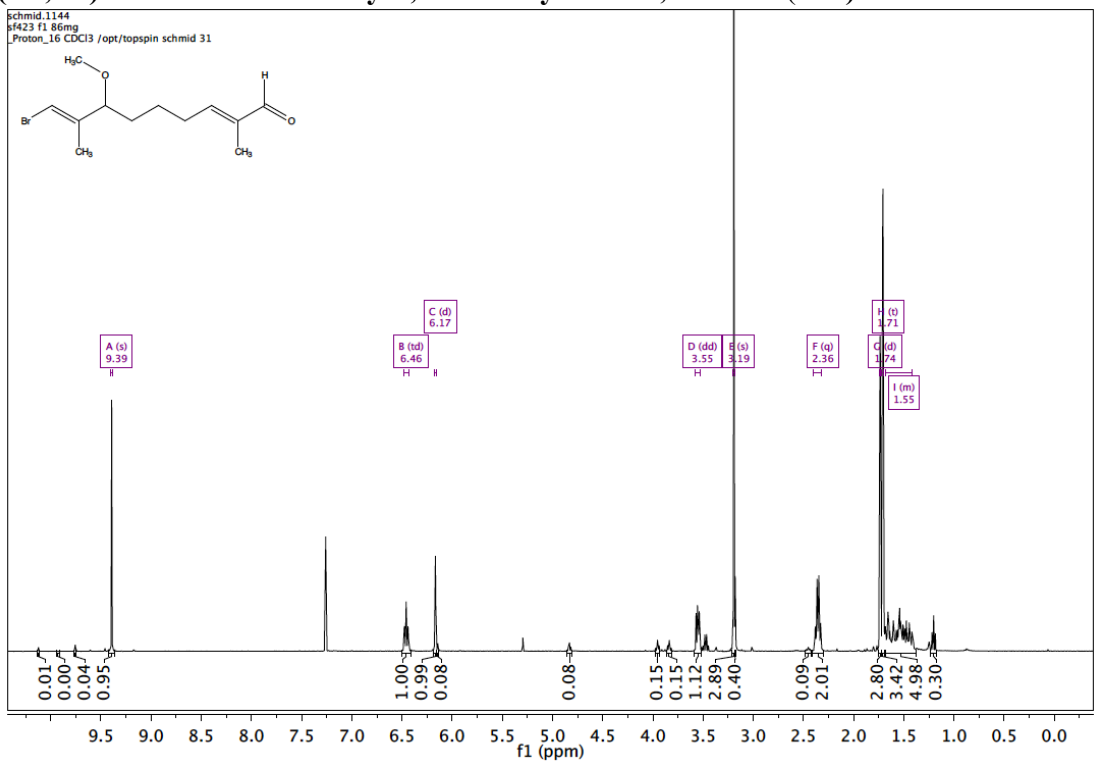



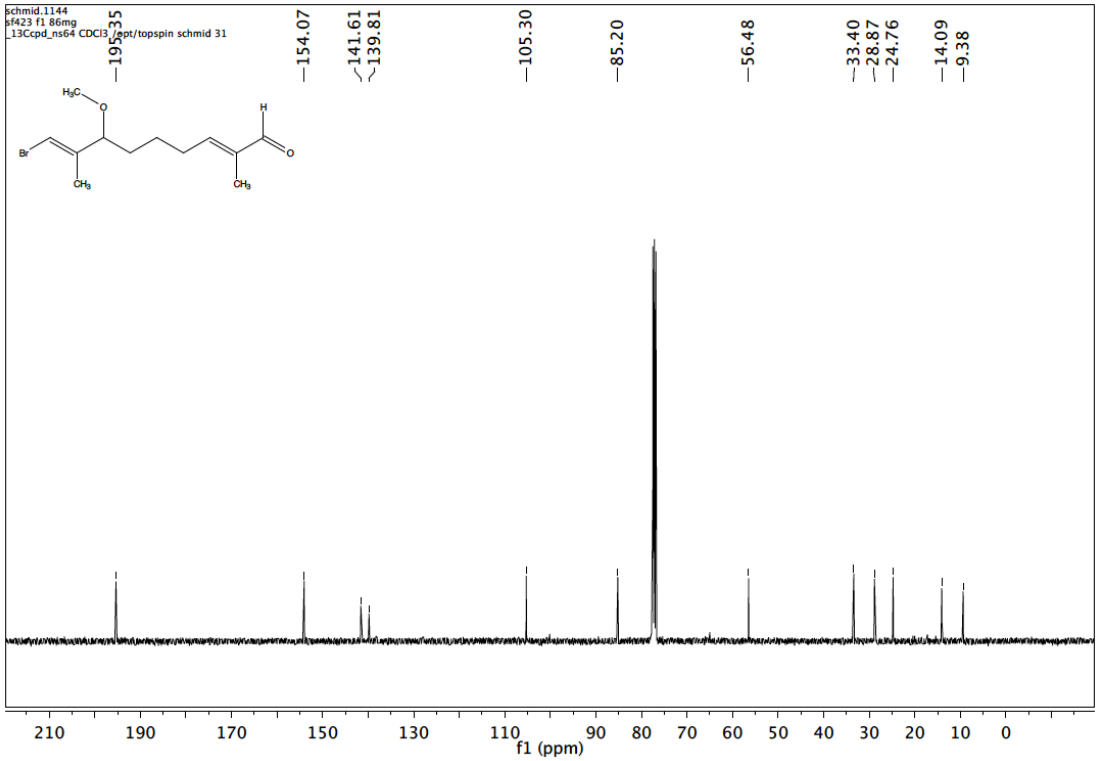
**(*E*)-2-(6-bromo-4-methoxy-5-methylhex-5-en-1-yl)-1,3-dioxolane (S16):**



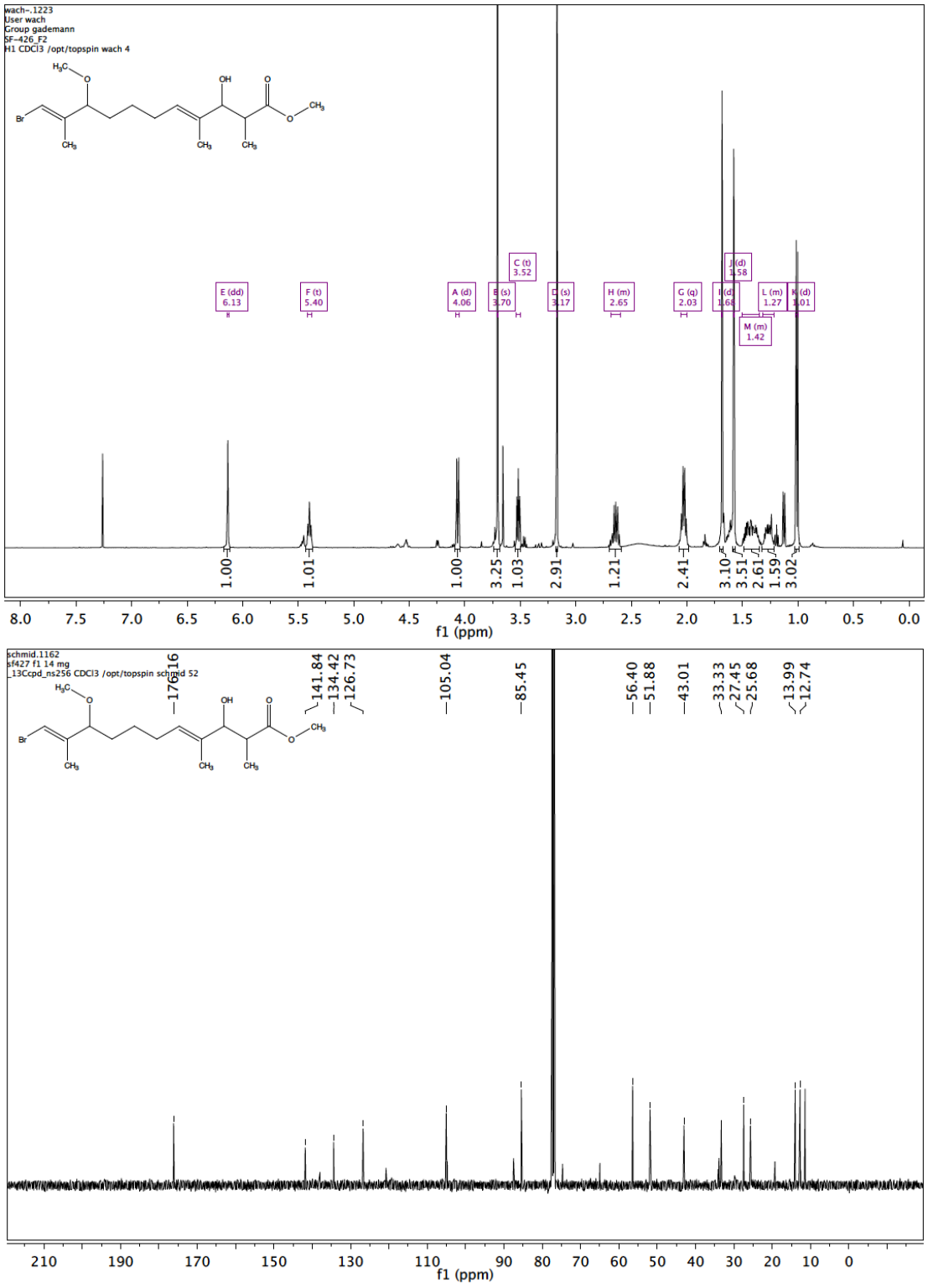



**(2*E*,8*E*)-9-bromo-7-methoxy-2,8-dimethylnona-2,8-dienal (S17):**

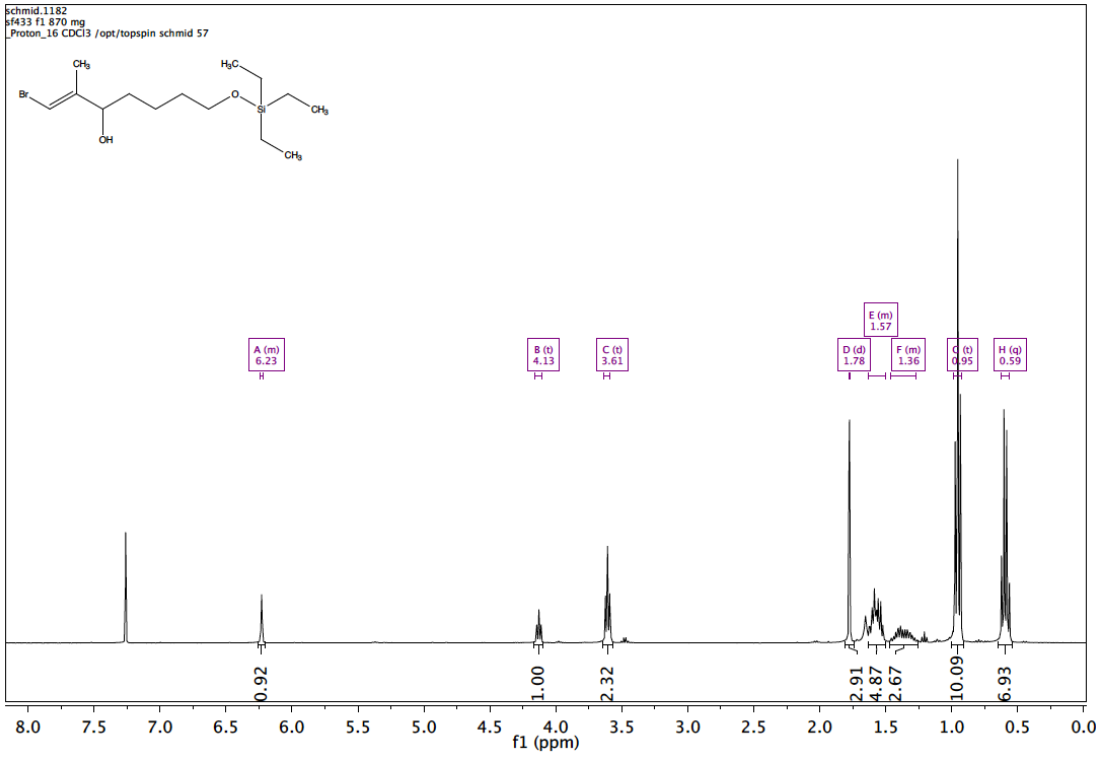


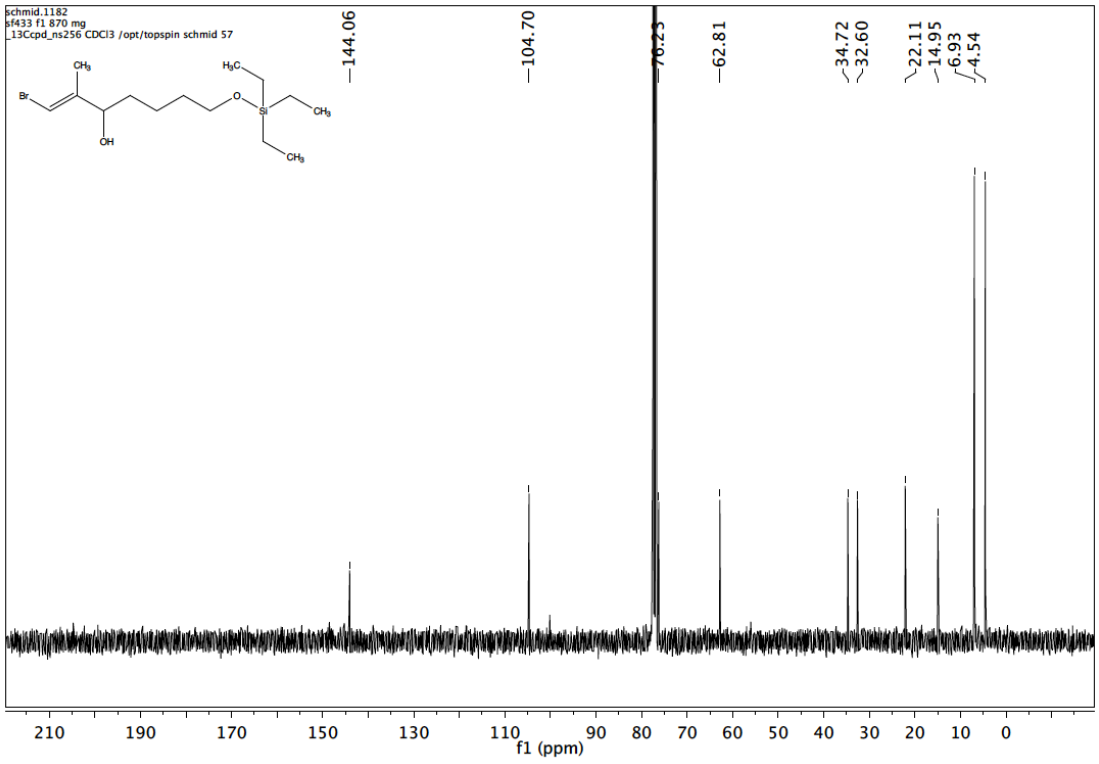



**(4*E*,10*E*)-methyl 11-bromo-3-hydroxy-9-methoxy-2,4,10-trimethylundeca-4,10-dienoate (3.71):**

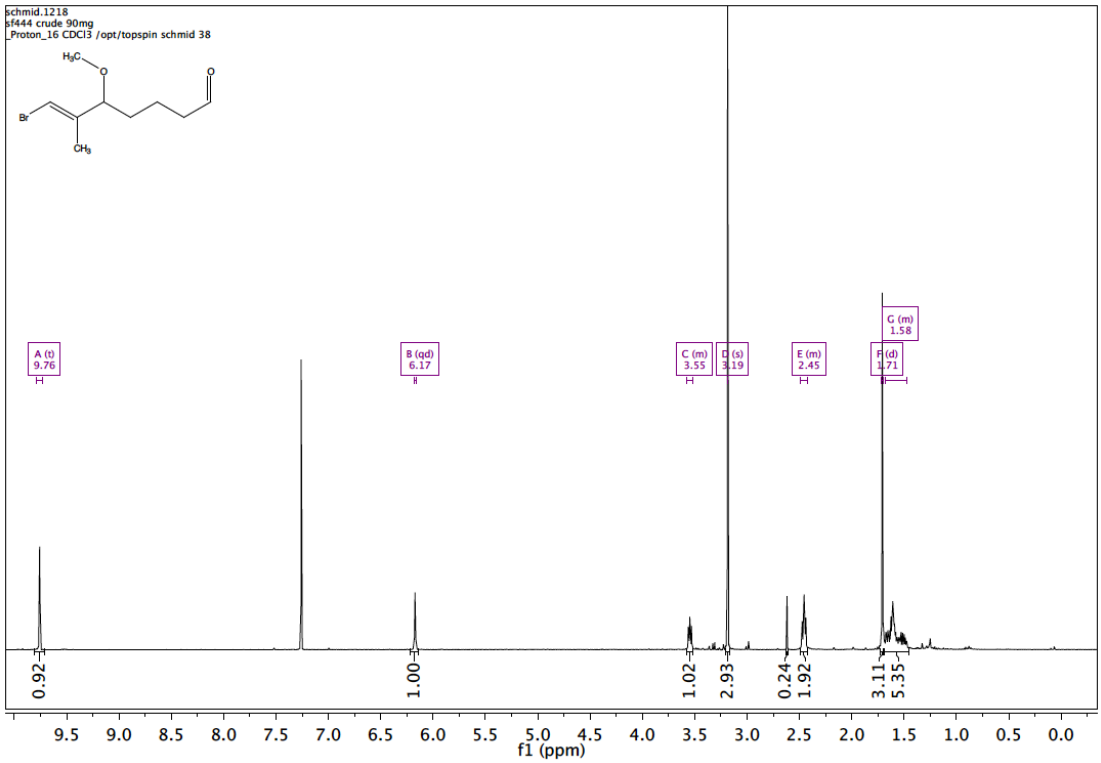


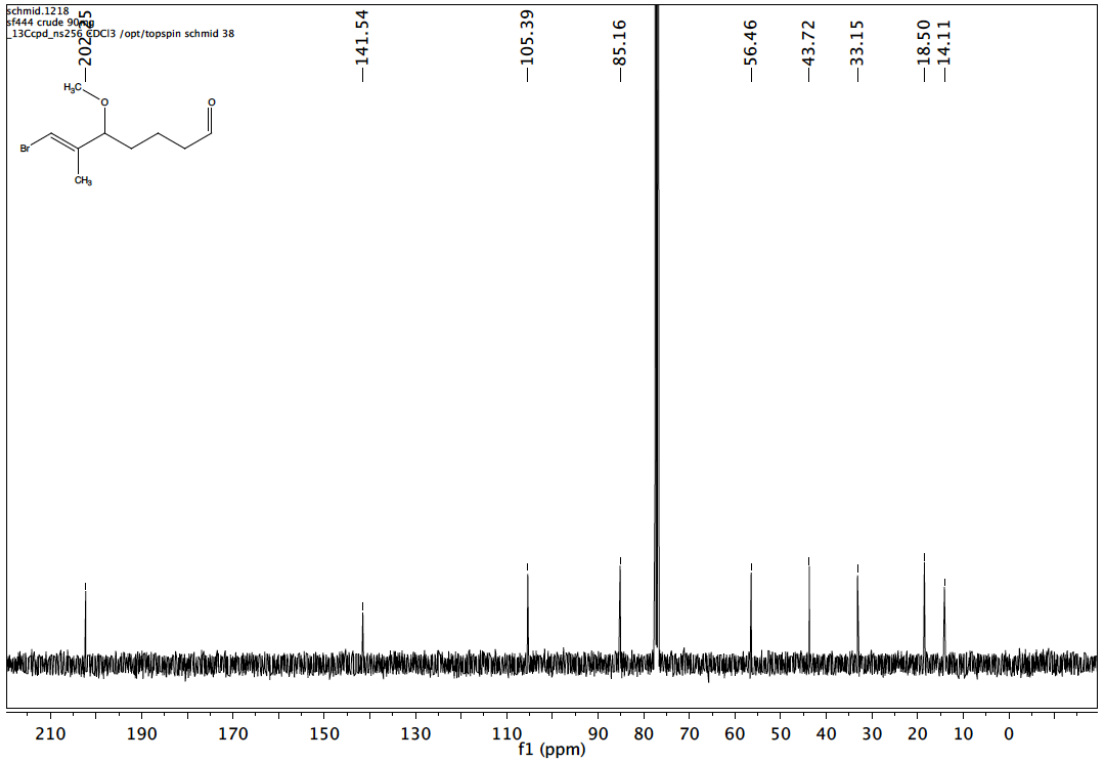
**(*E*)-1-bromo-2-methyl-7-((triethylsilyl)oxy)hept-1-en-3-ol (S19):**



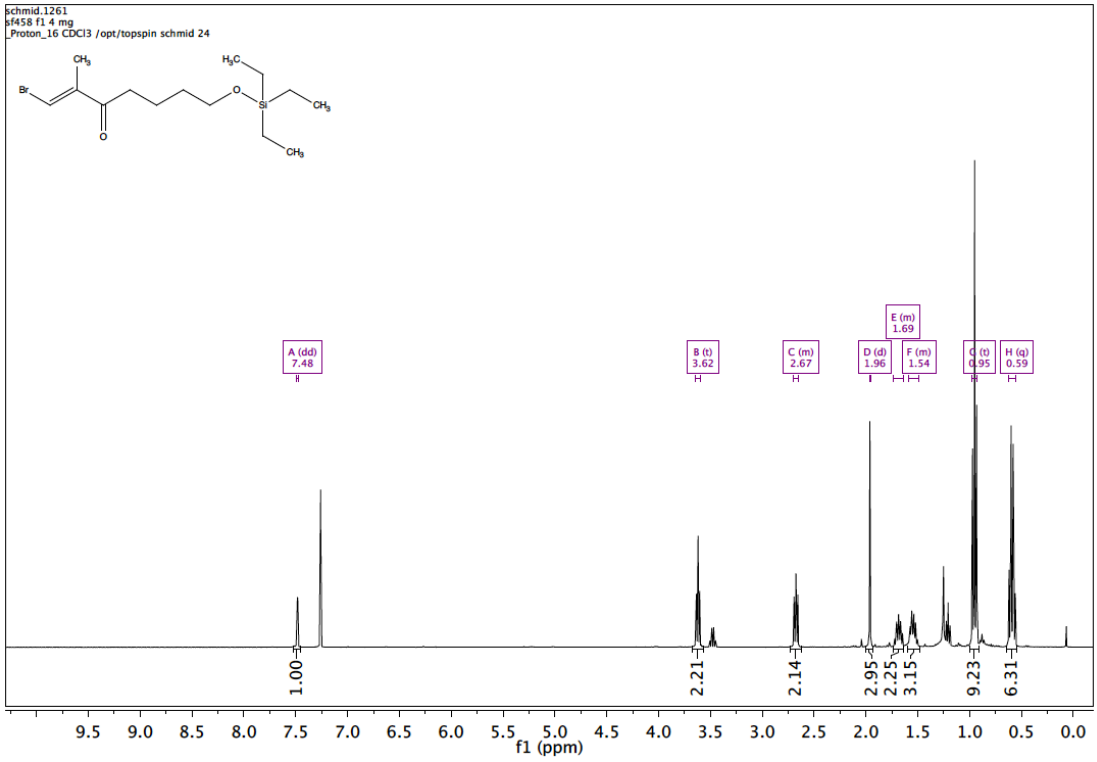



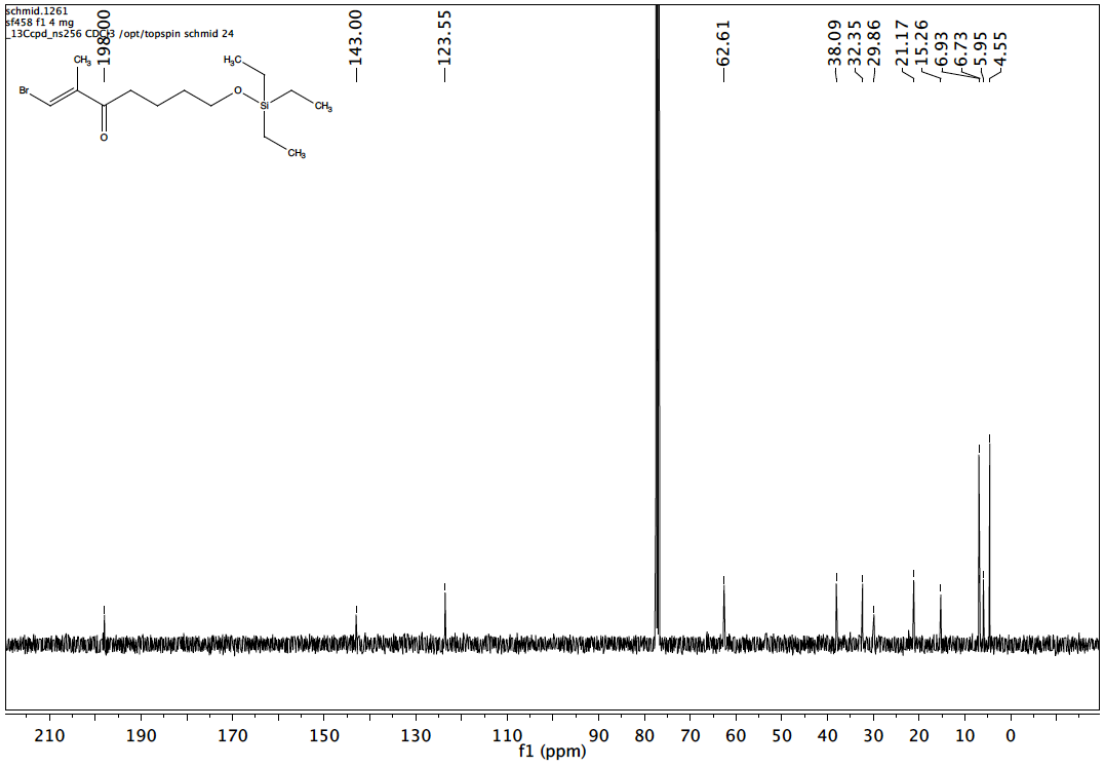
**(*E*)-7-bromo-5-methoxy-6-methylhept-6-enal (3.70):**



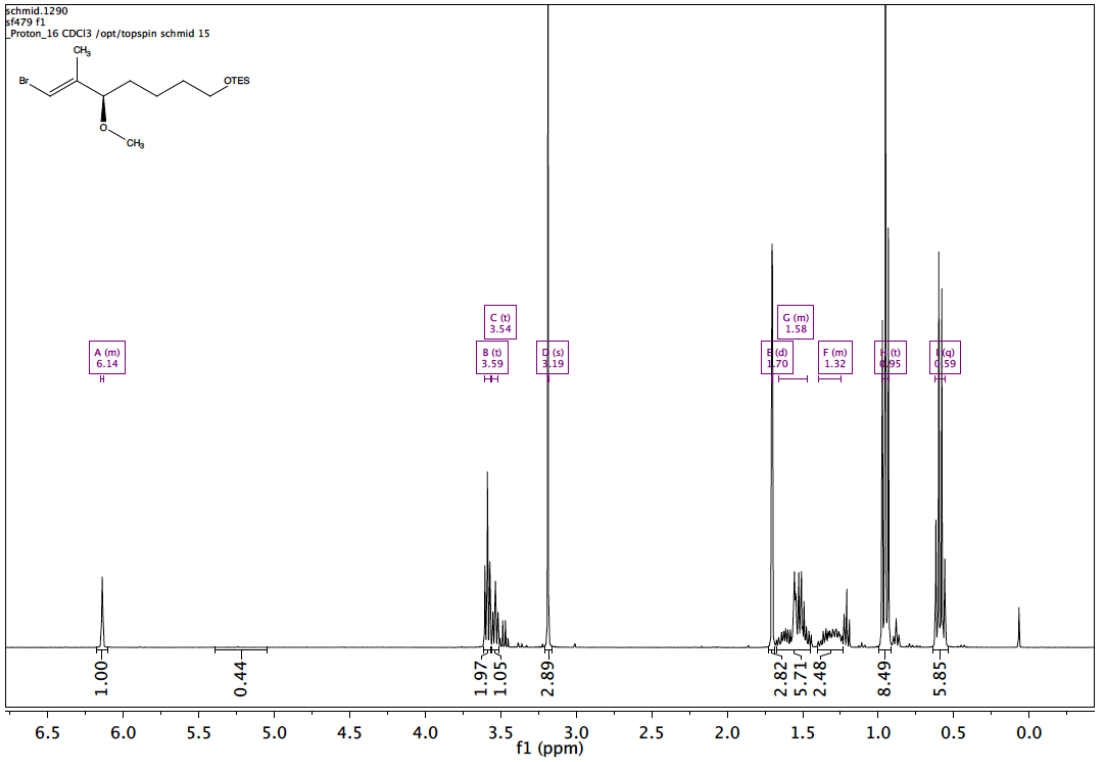



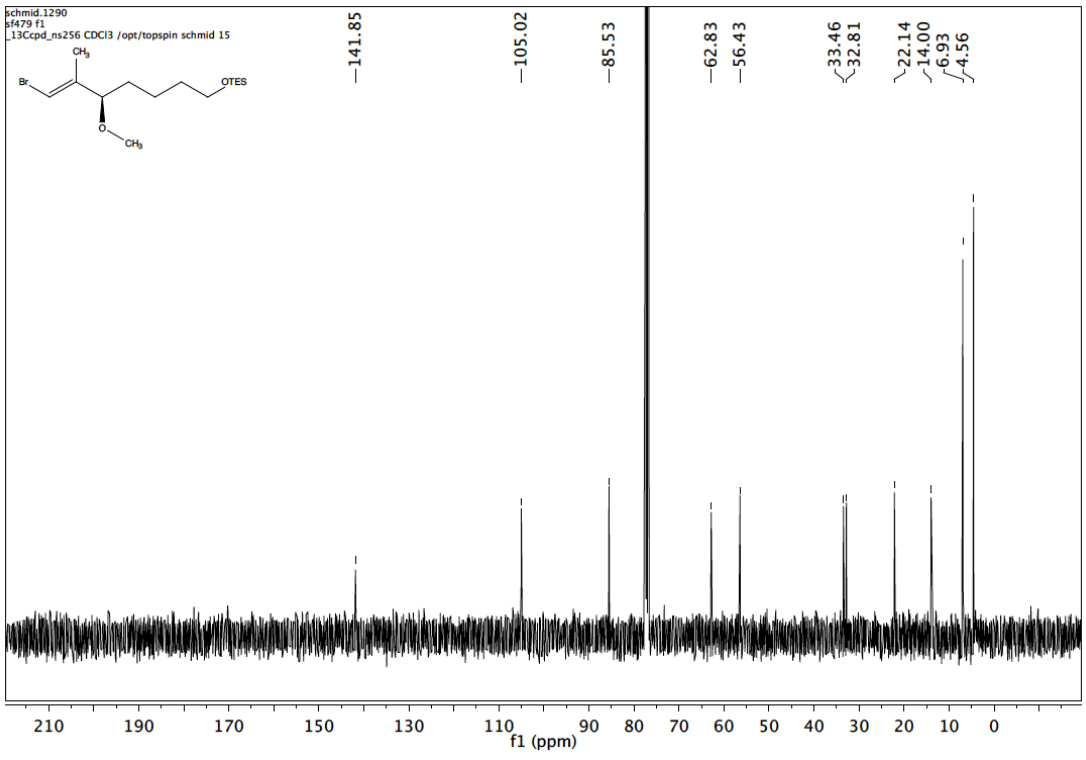
**(*E*)-1-bromo-2-methyl-7-((triethylsilyl)oxy)hept-1-en-3-one (S21)**:



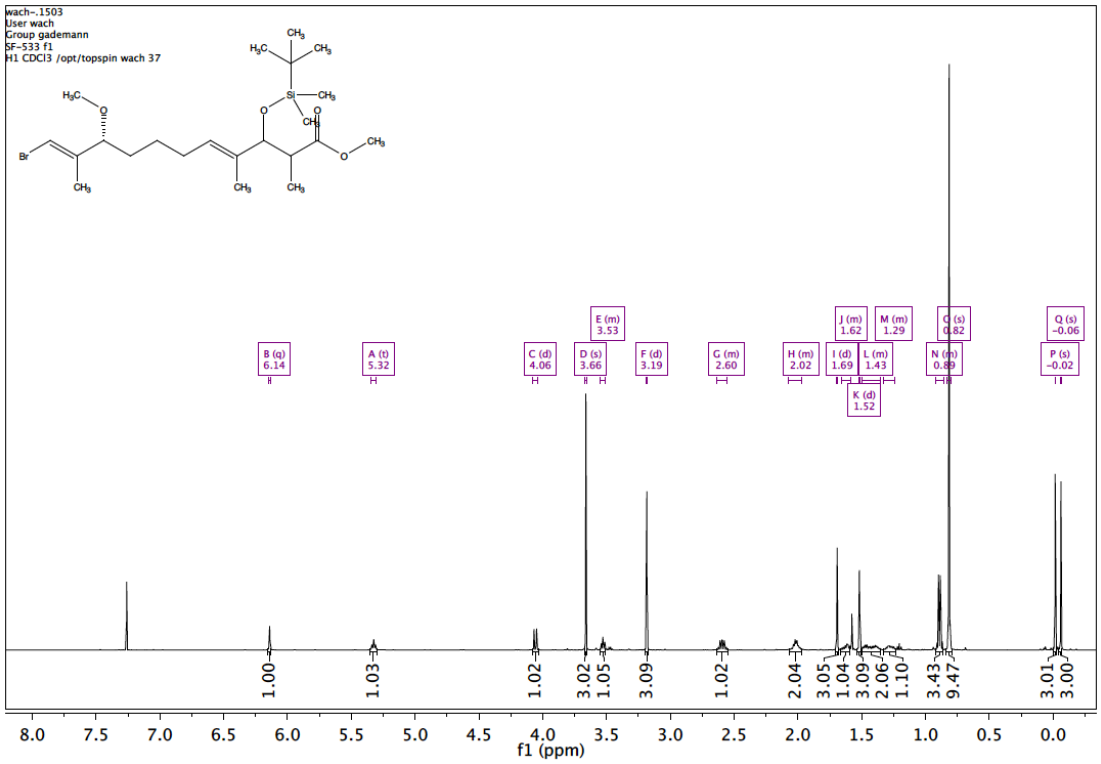



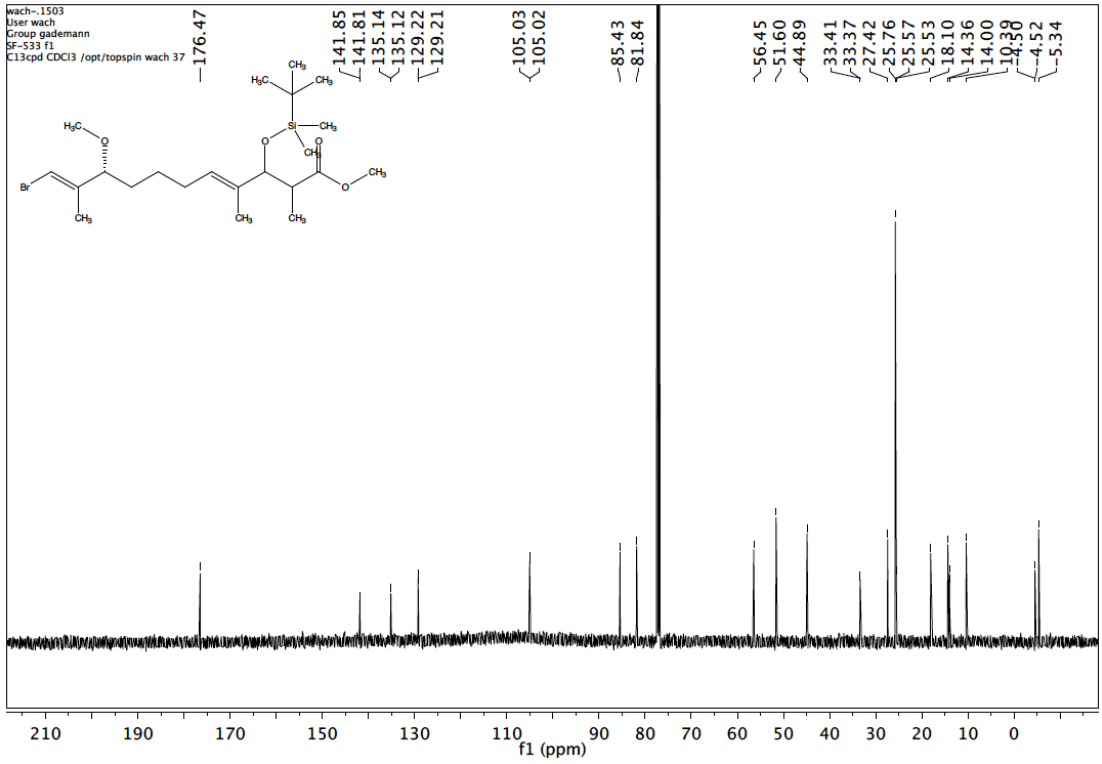
**(*R*,*E*)-((7-bromo-5-methoxy-6-methylhept-6-en-1-yl)oxy)triethylsilane (S43)**:



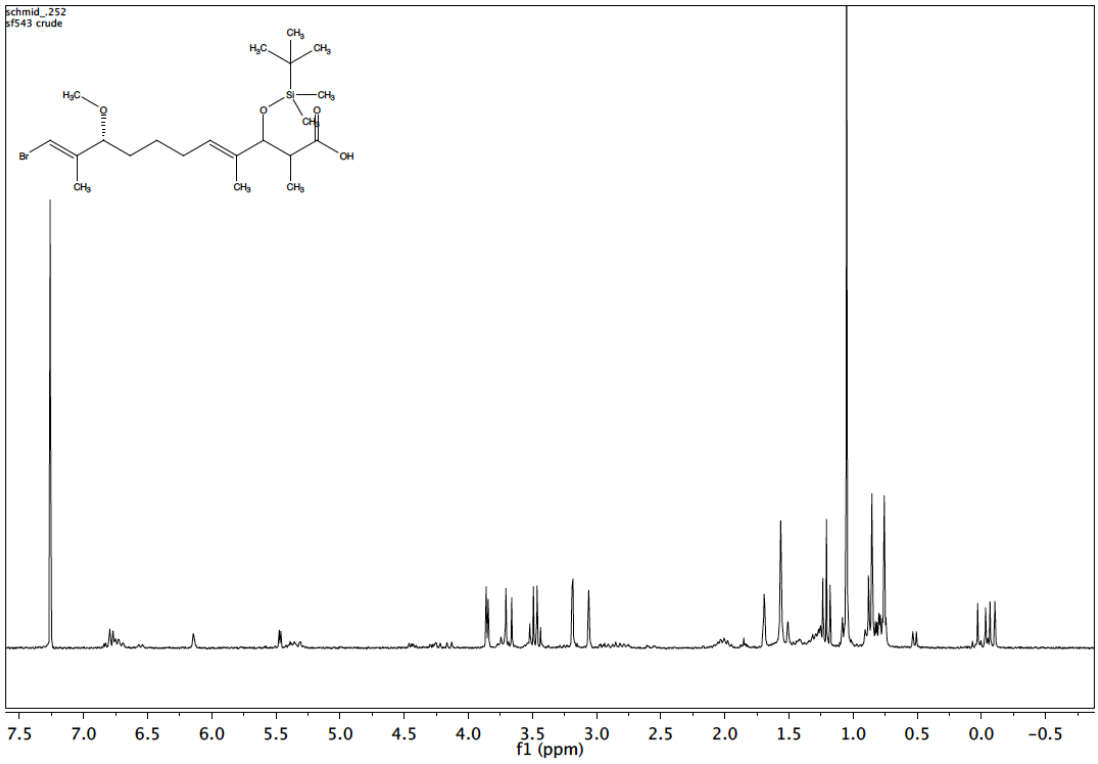



**(4*E*,9*R*,10*E*)-methyl 11-bromo-3-((*tert*-butyldimethylsilyl)oxy)-9-methoxy-2,4,10-trimethylundeca-4,10-dienoate (S24):**

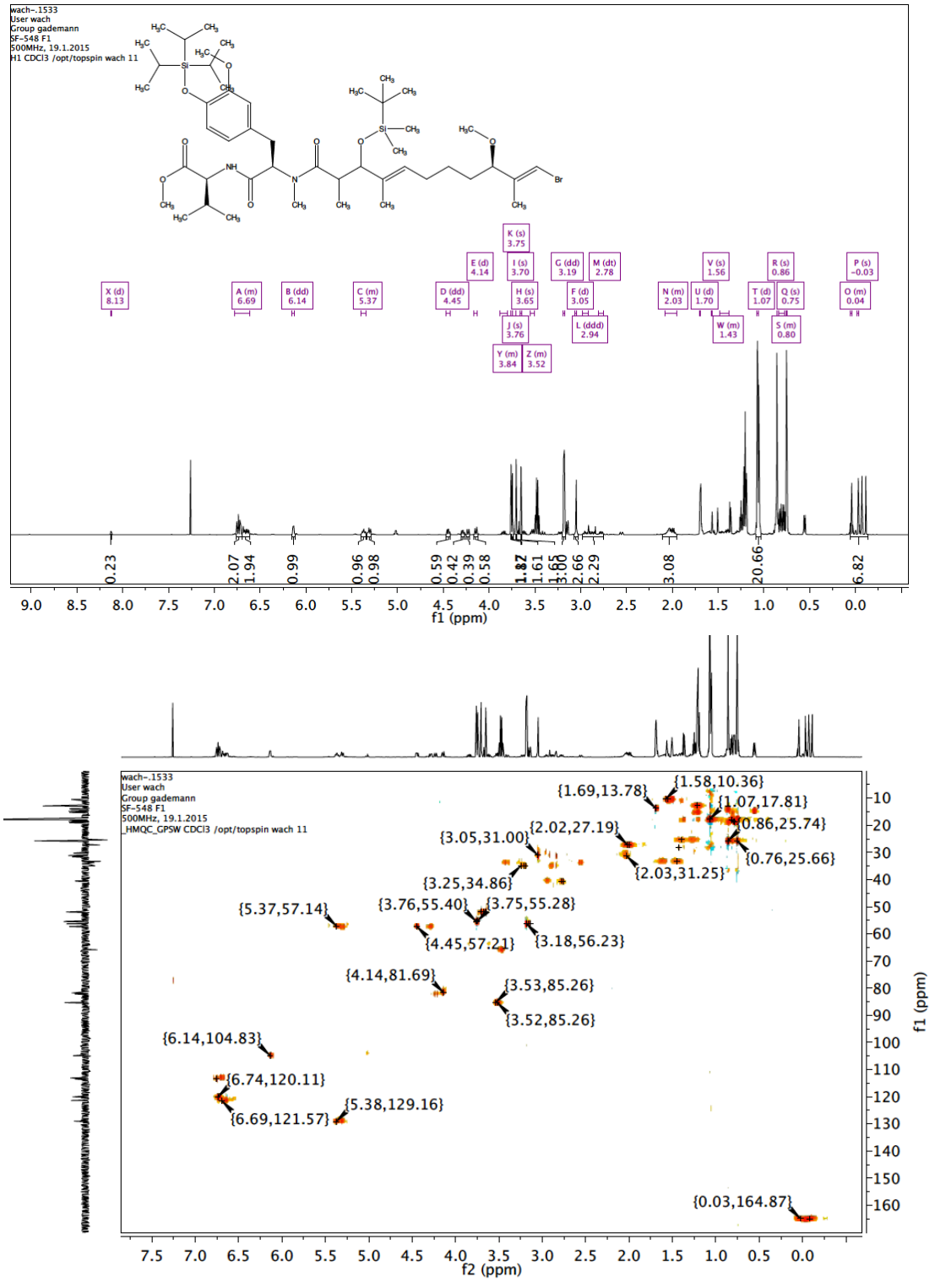


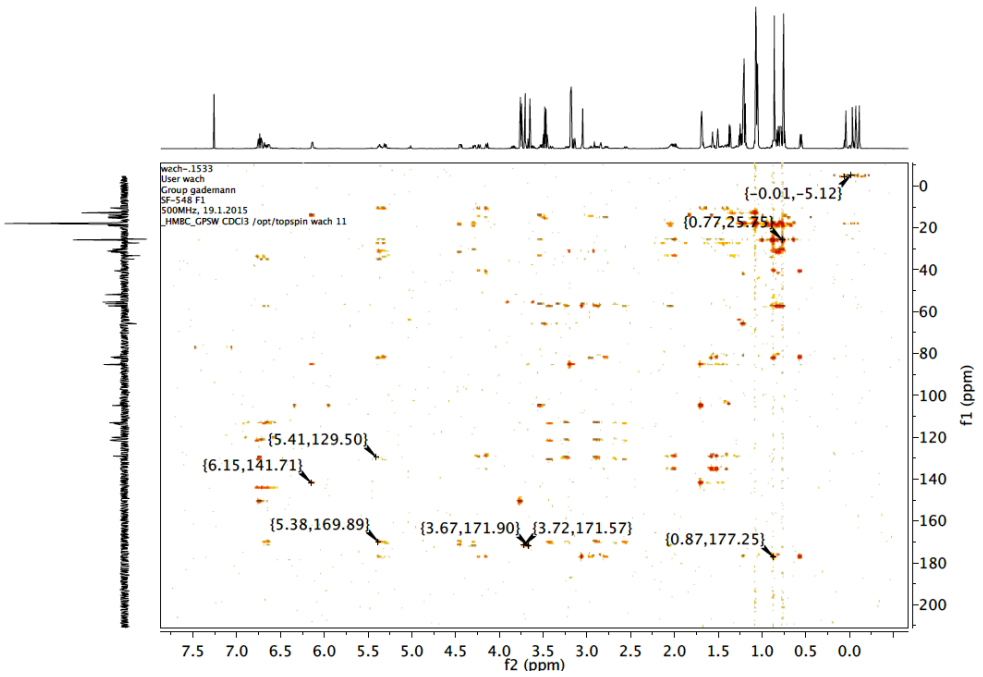



**(4*E*,9*R*,10*E*)-11-bromo-3-((*tert*-butyldimethylsilyl)oxy)-9-methoxy-2,4,10-trimethylundeca-4,10-dienoic acid (3.117):**



**(9*R*,12*S*)-methyl 5-((*R*,2*E*,8*E*)-9-bromo-7-methoxy-8-methylnona-2,8-dien-2-yl)-12-isopropyl-9-(3-methoxy-4-((triisopropylsilyl)oxy)benzyl)-2,2,3,3,6,8-hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate (3.118):**

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User wach
Group gademann
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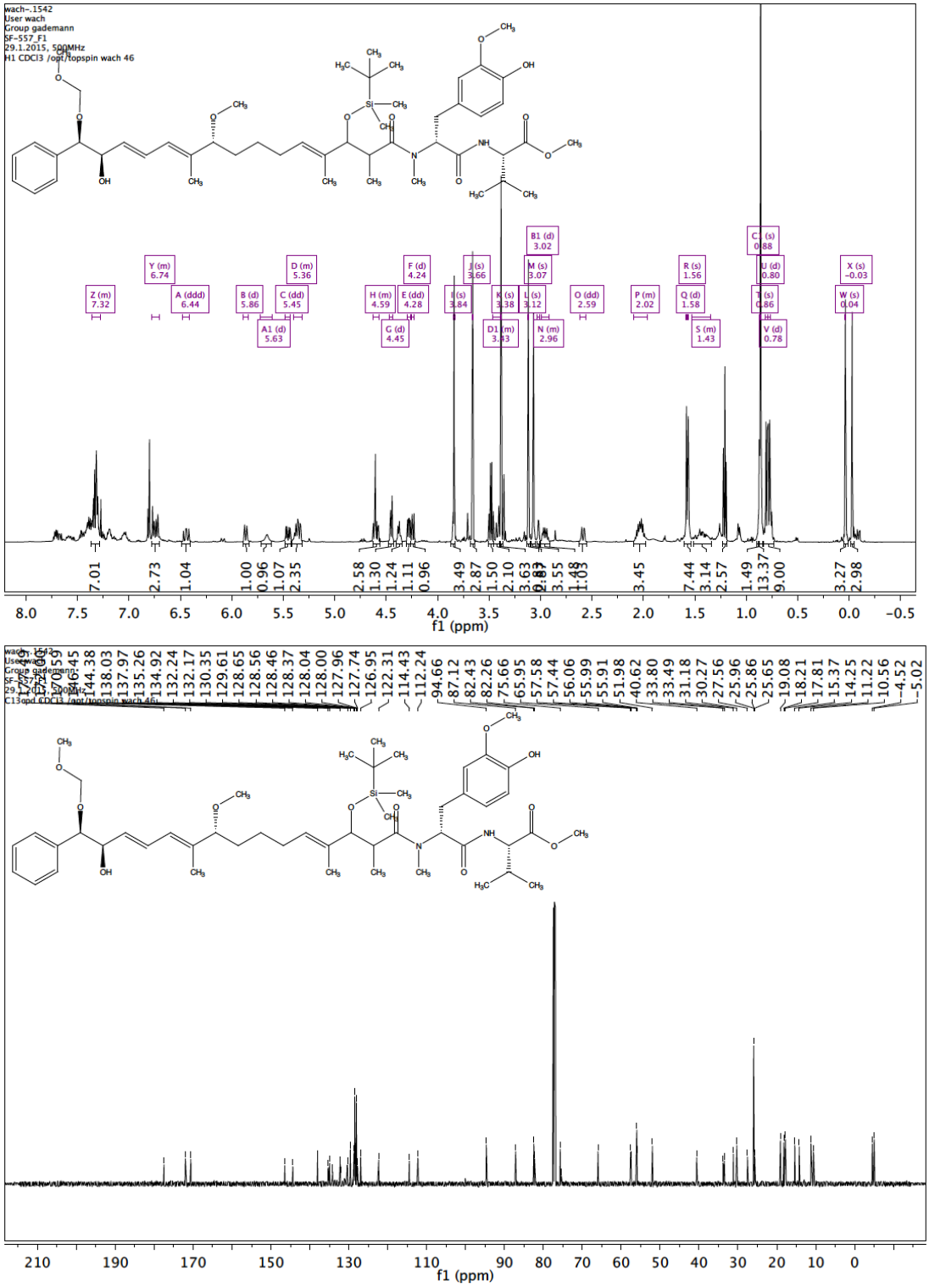
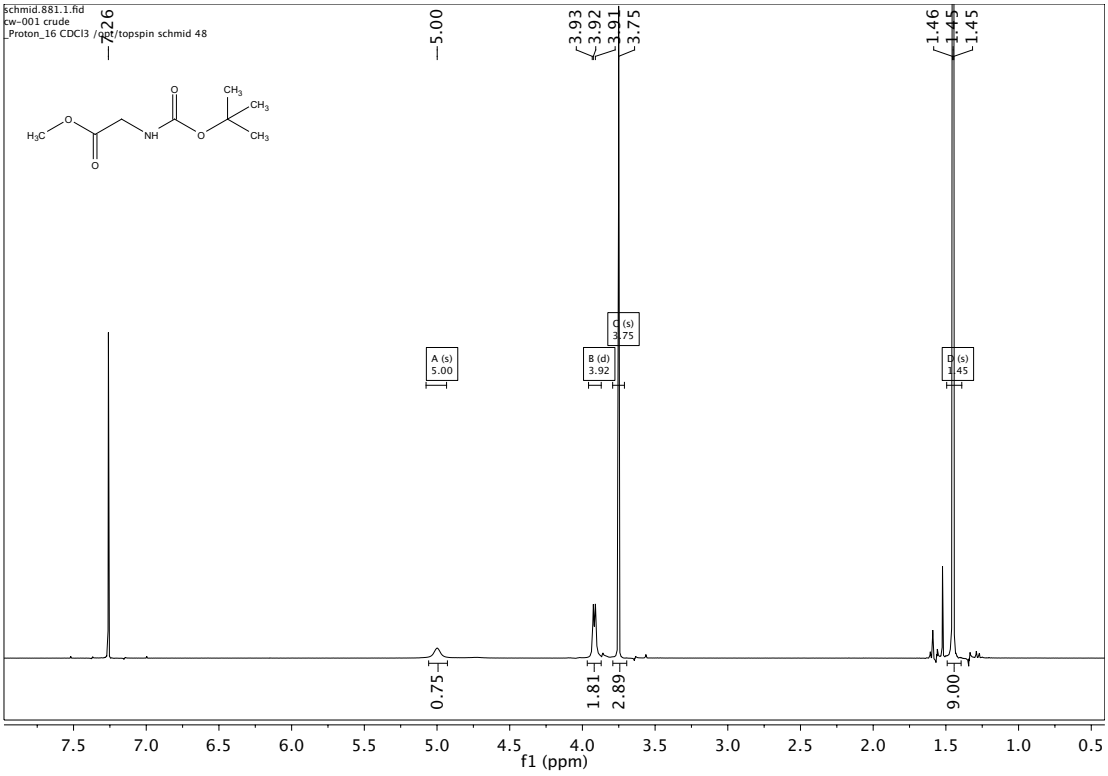
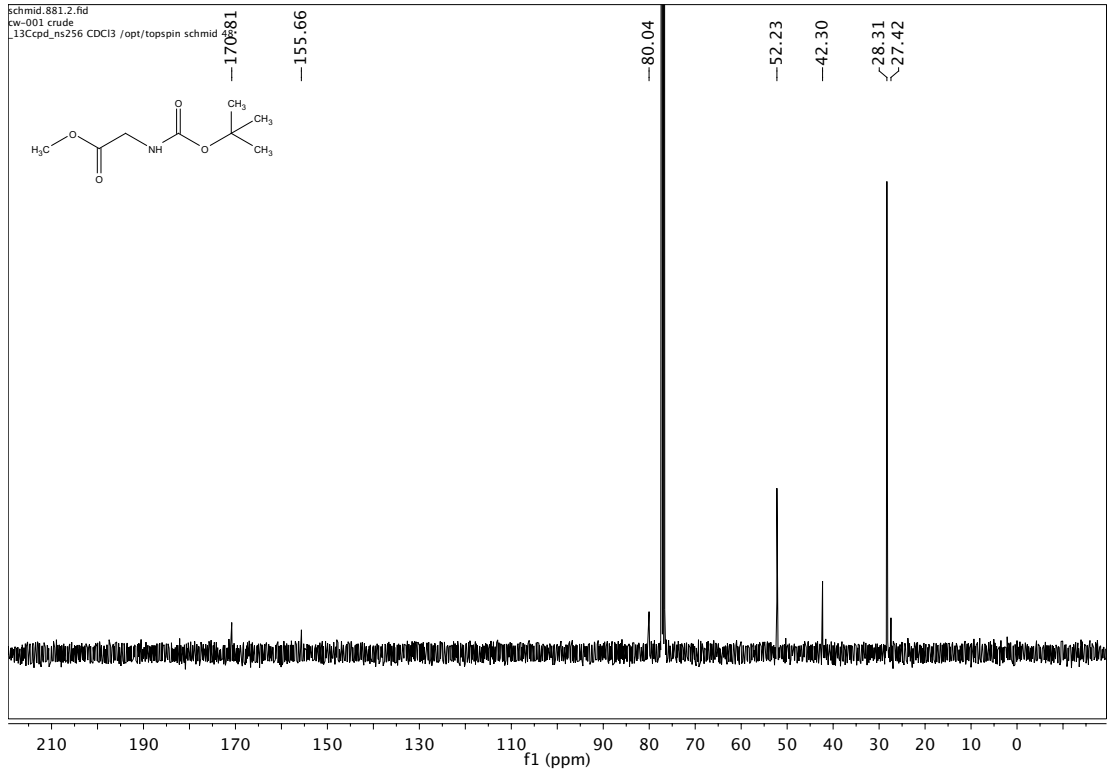
{0.77,25.75}
{5.41,129.50}
{6.15,141.71}
{5.38,169.89}
{3.67,171.90}
{3.72,171.57}
{0.87,177.25}
f1 (ppm)
f2 (ppm)

**(5*R*,6*R*,7*E*,9*E*,11*R*,15*E*,21*R*,24*S*)-methyl 17-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-21-(4-hydroxy-3-methoxybenzyl)-24-isopropyl-11-methoxy-10,16,18,20-tetramethyl-19,22-dioxo-5-phenyl-2,4-dioxa-20,23-diazapentacosa-7,9,15-trien-25-oate (3.120):**

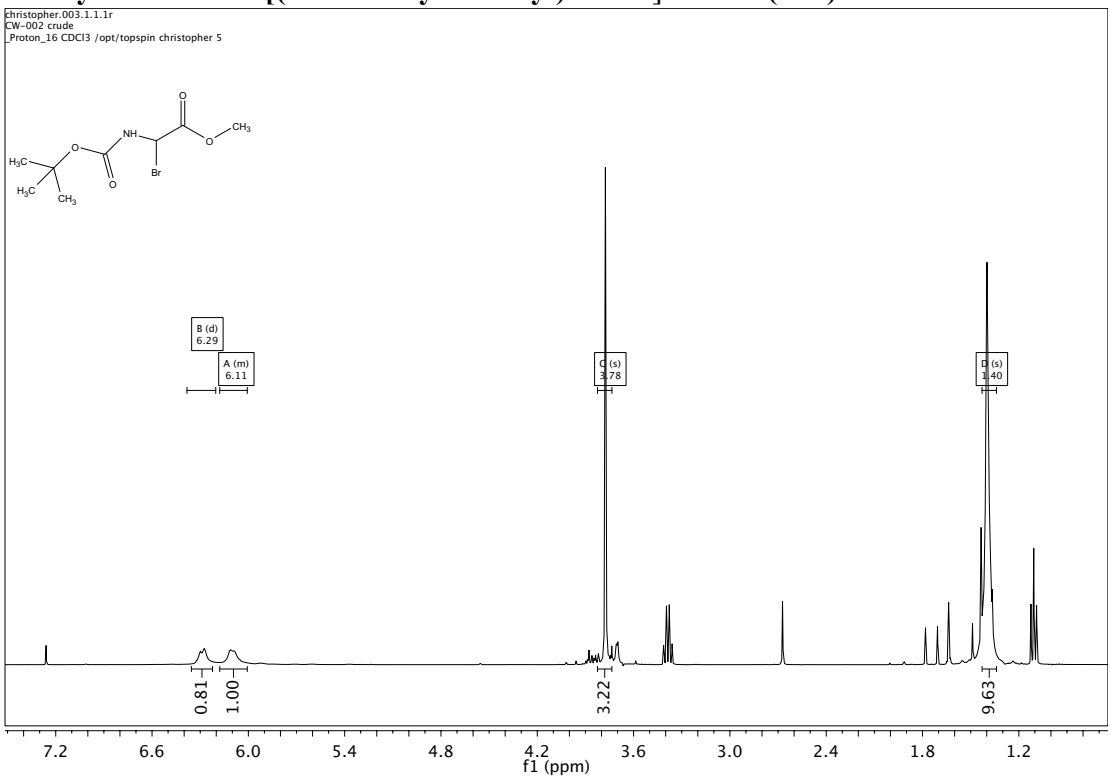


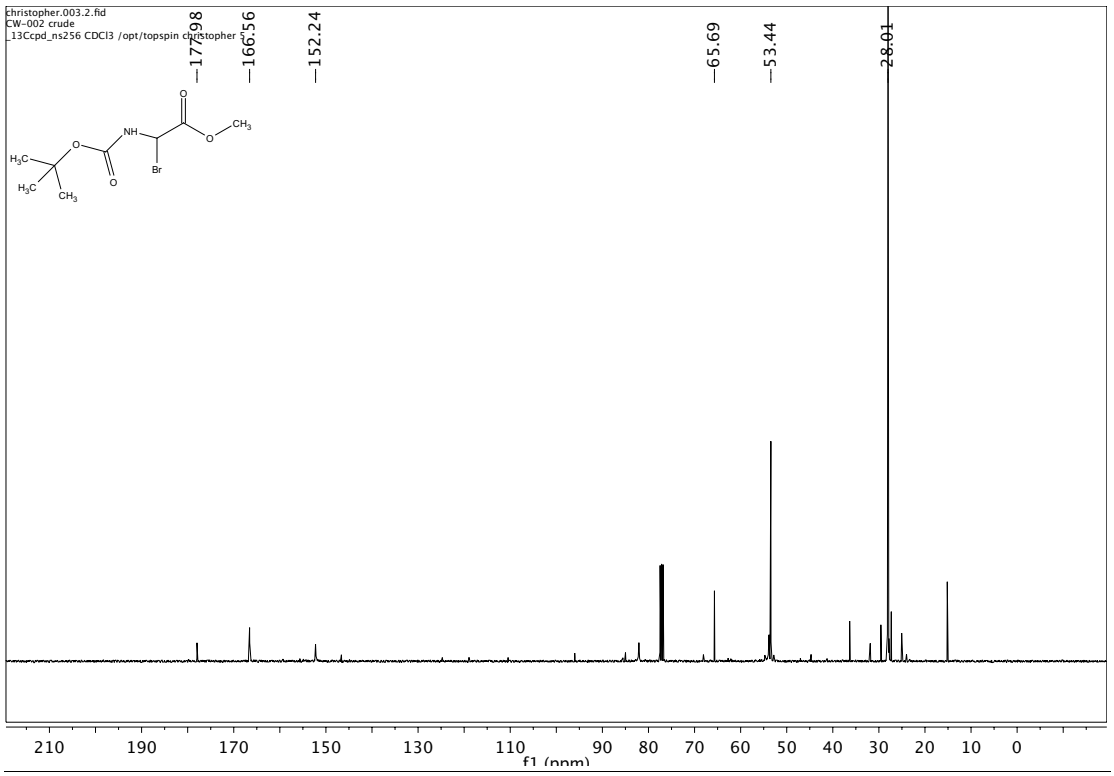
## **Methyl (*tert*-butoxycarbonyl)glycinate** (**S25**):



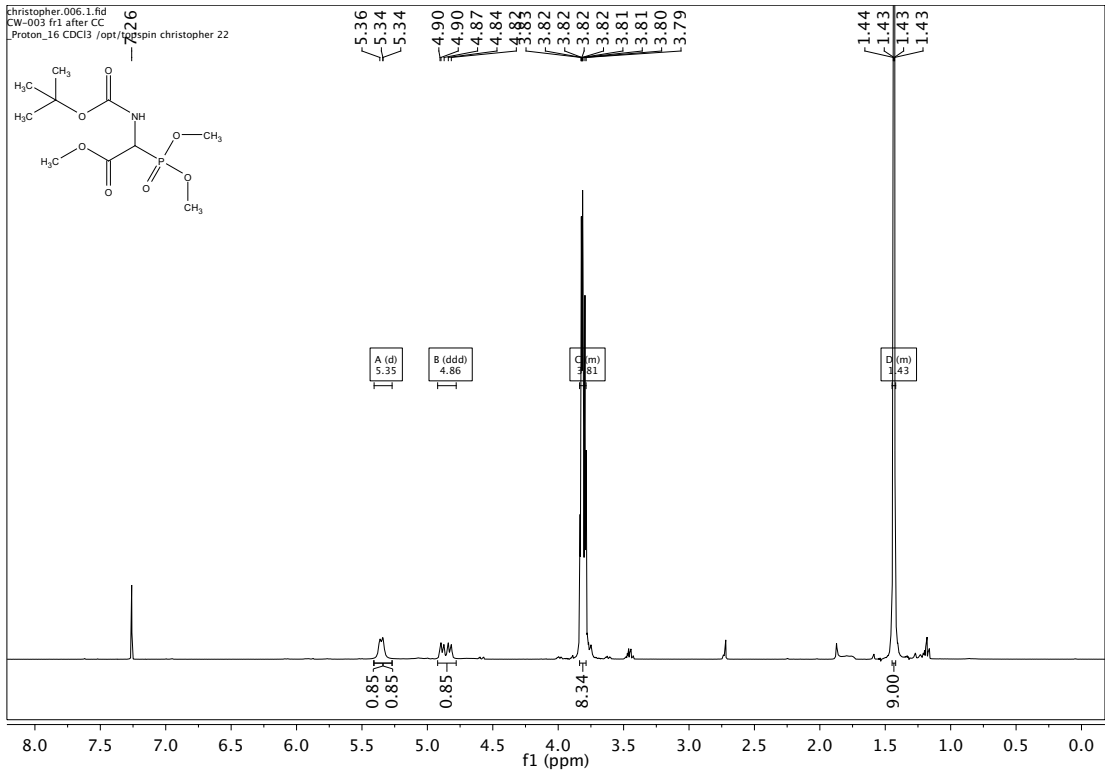



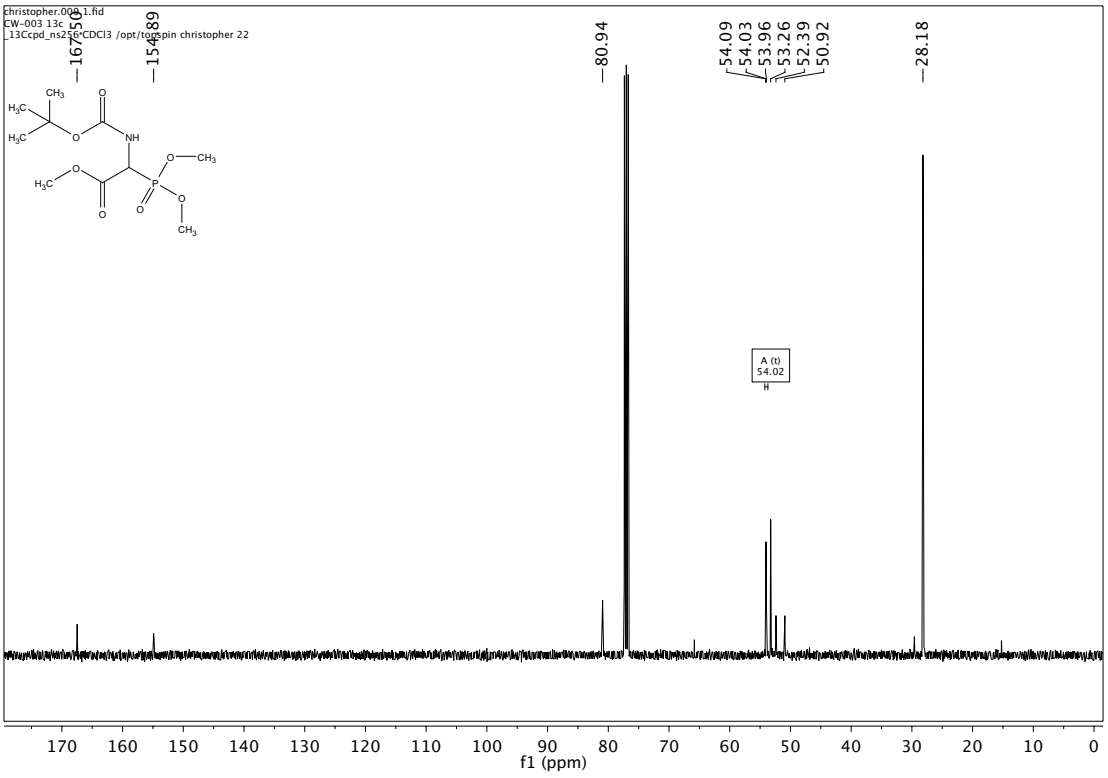
**Methyl 2-bromo-2-[(*tert*-butoxycarbonyl)amino]acetate (S26):**



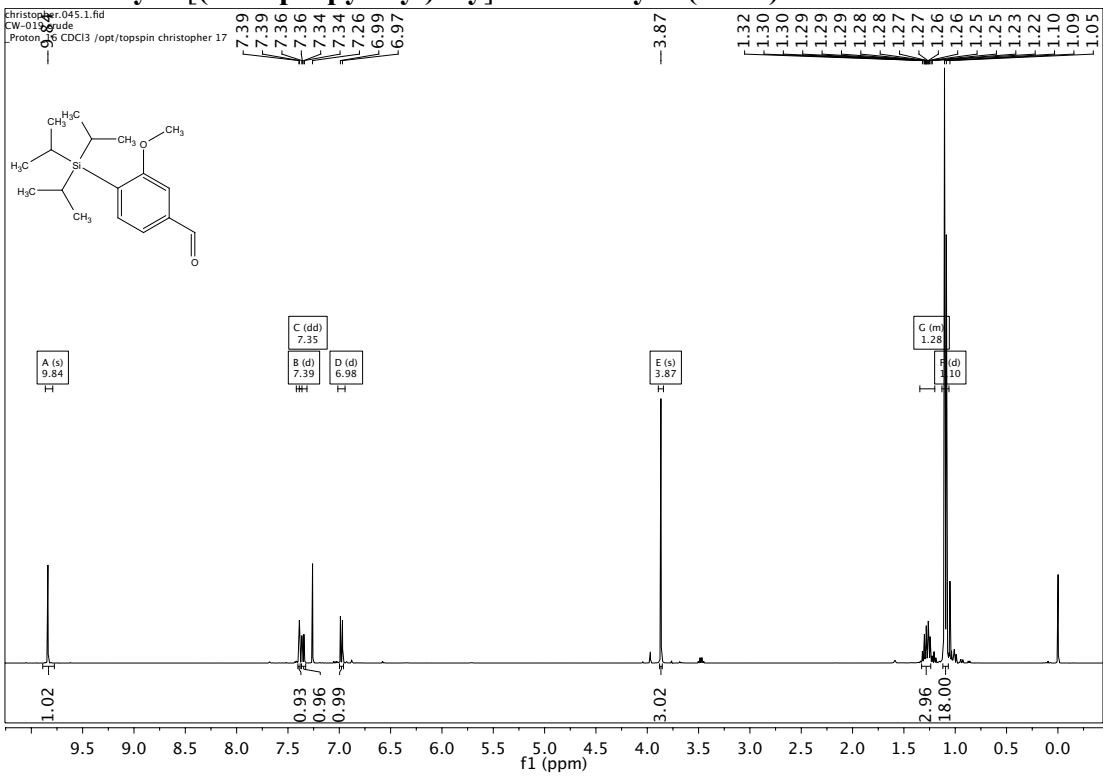



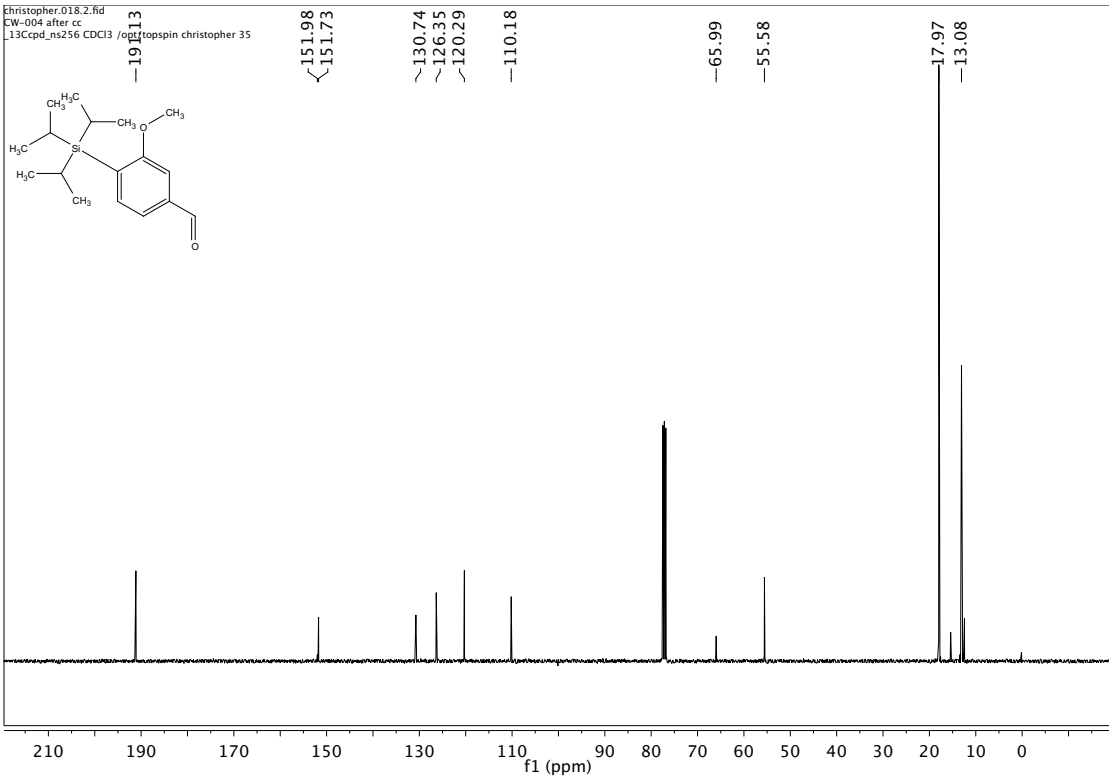
**Methyl 2-[(*tert*-butoxycarbonyl)amino]-2-(dimethoxyphosphoryl)acetate (3.97):**



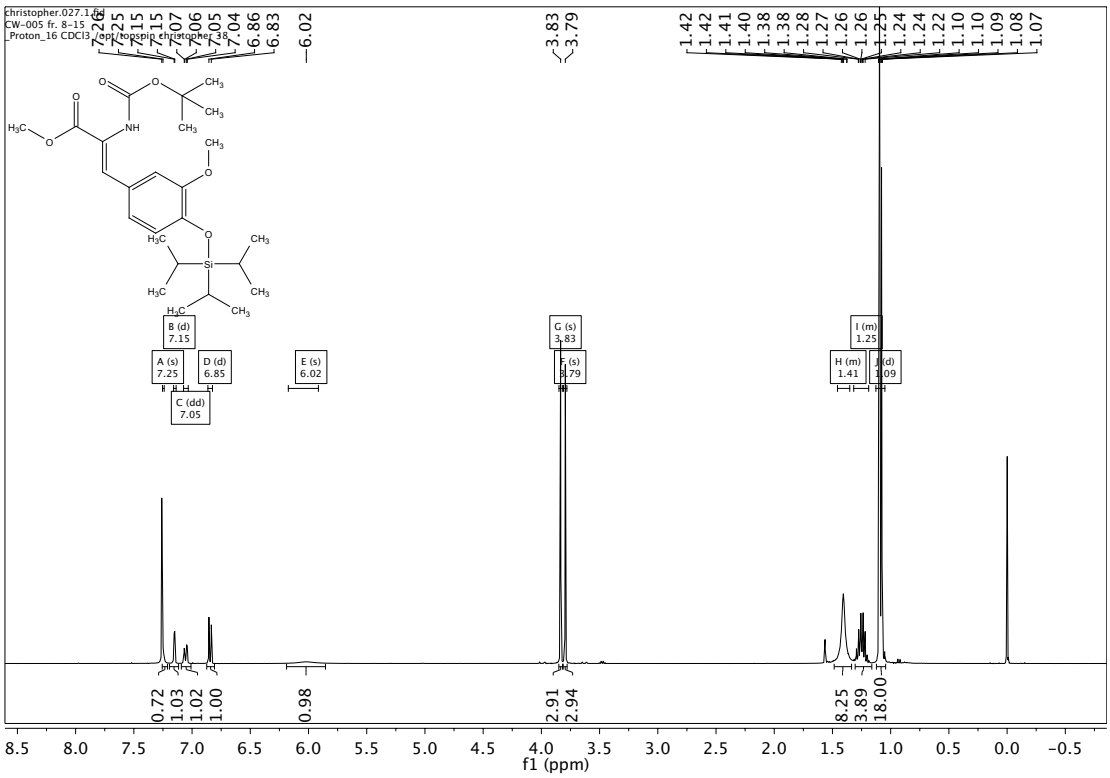



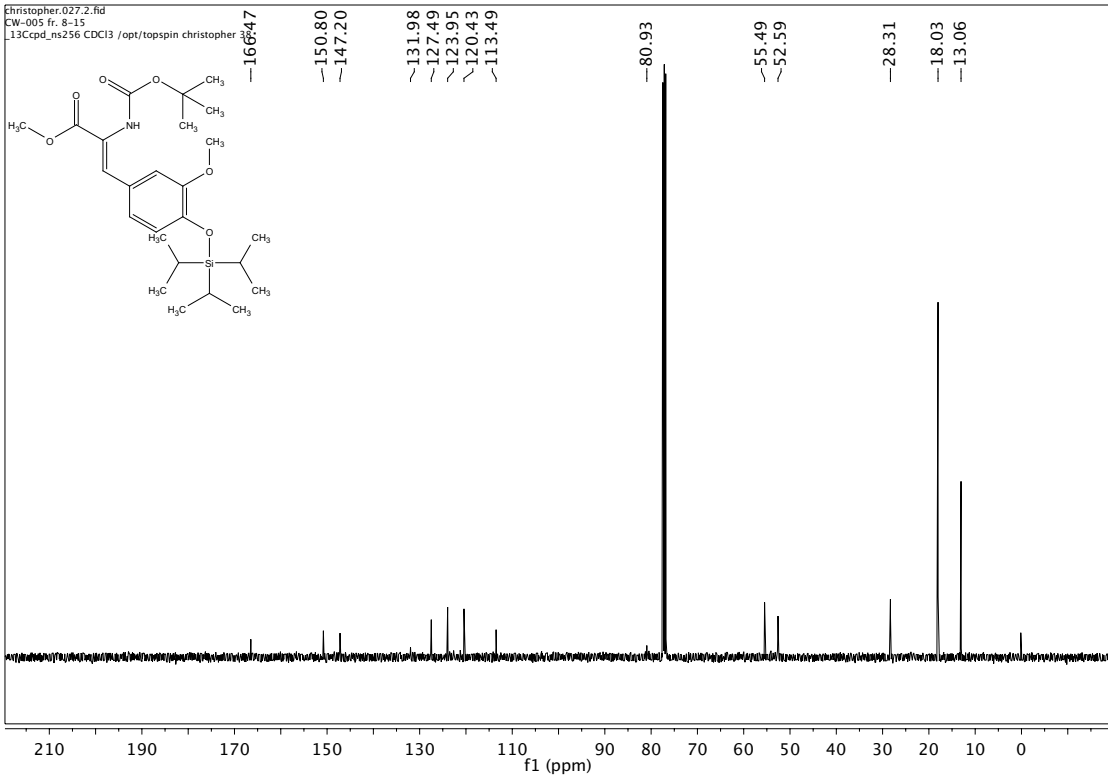
## 3-Methoxy-4-[(triisopropylsilyl)oxy]benzaldehyde (3.101):



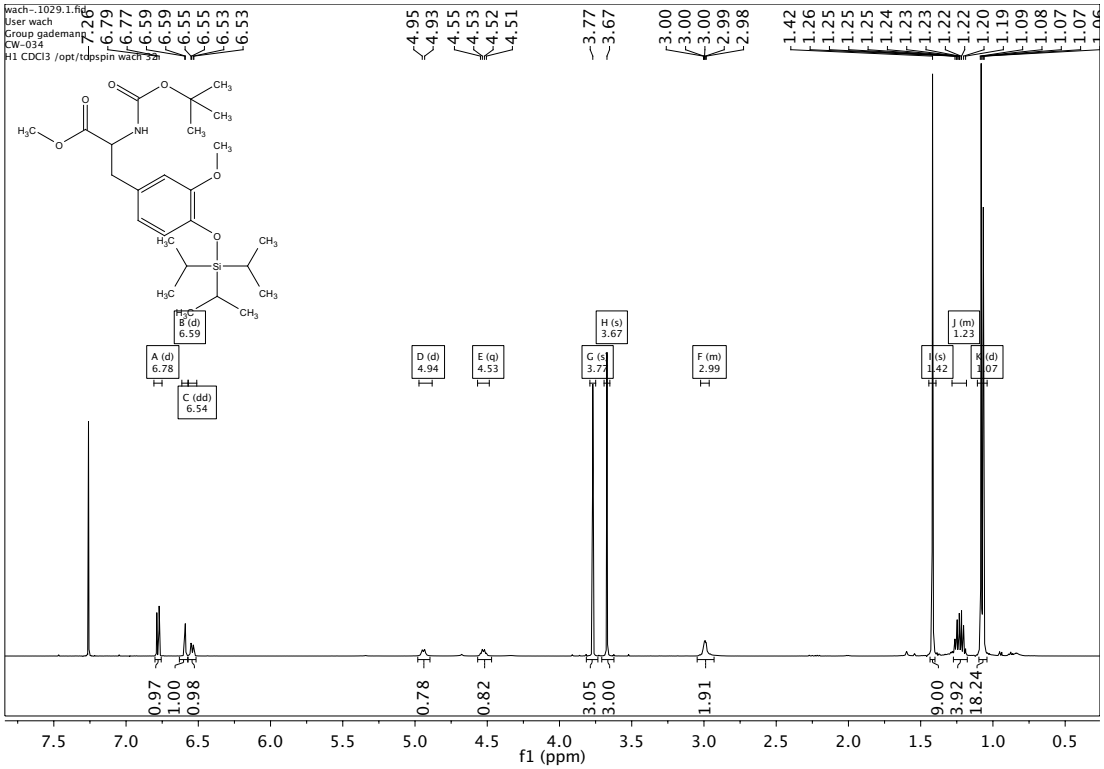



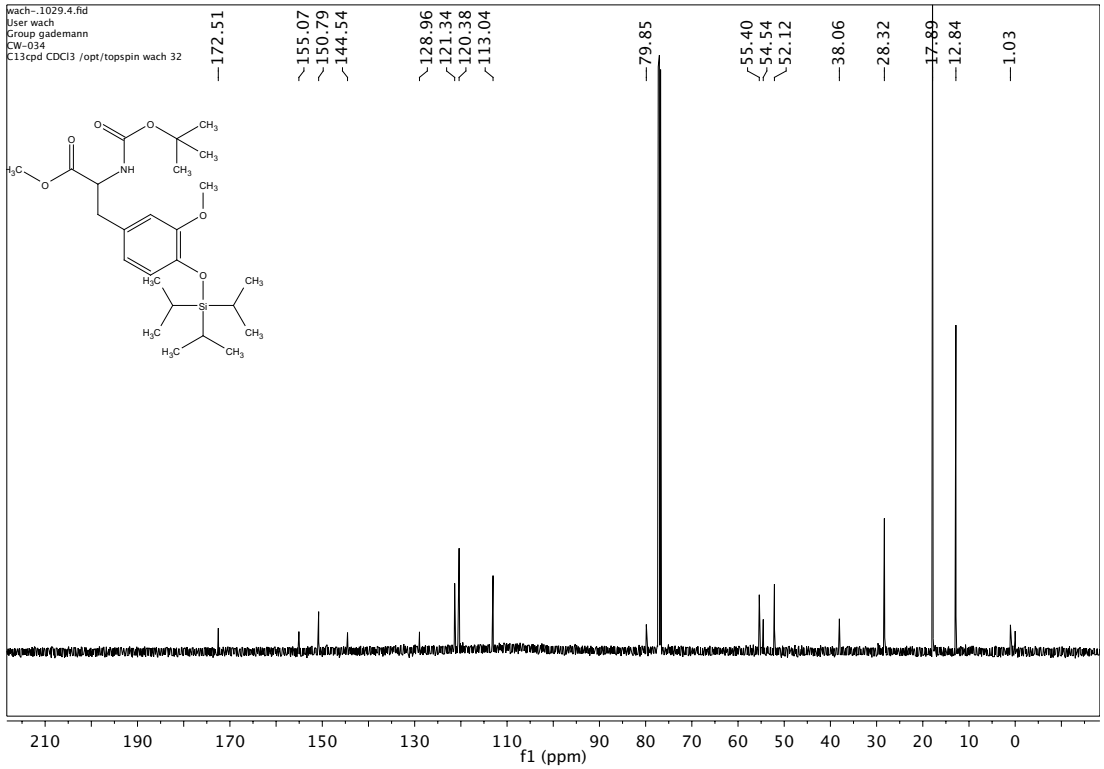
**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}acrylate (3.98):**



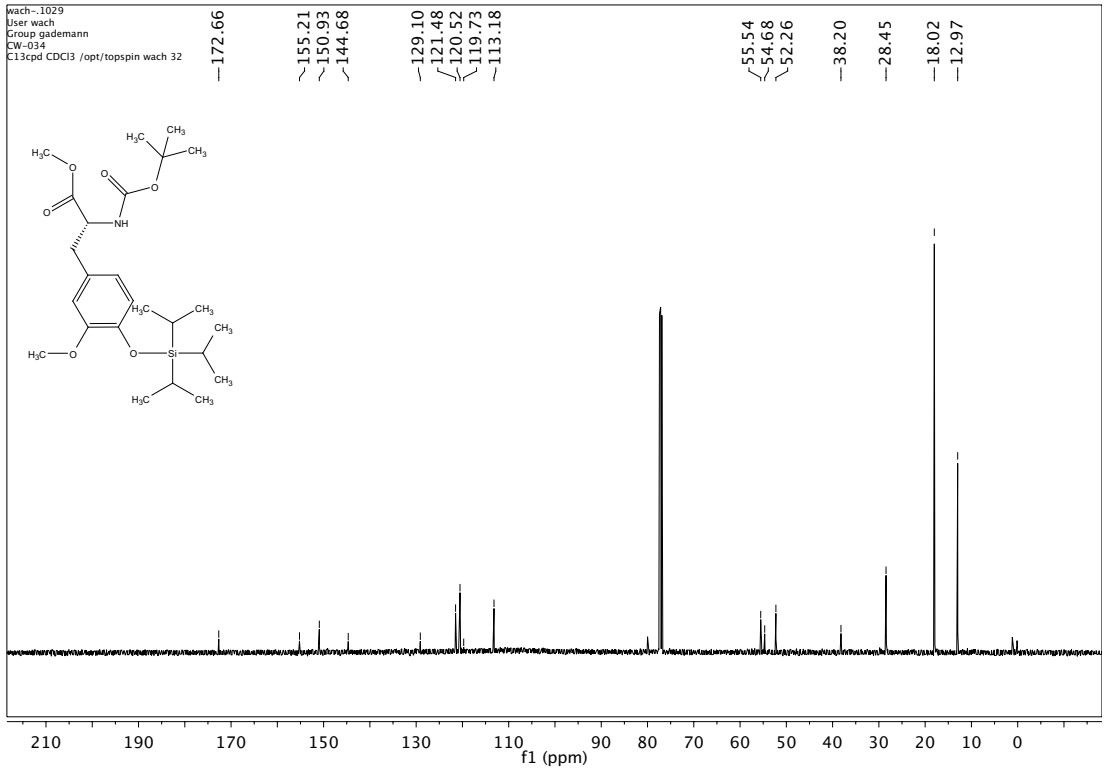



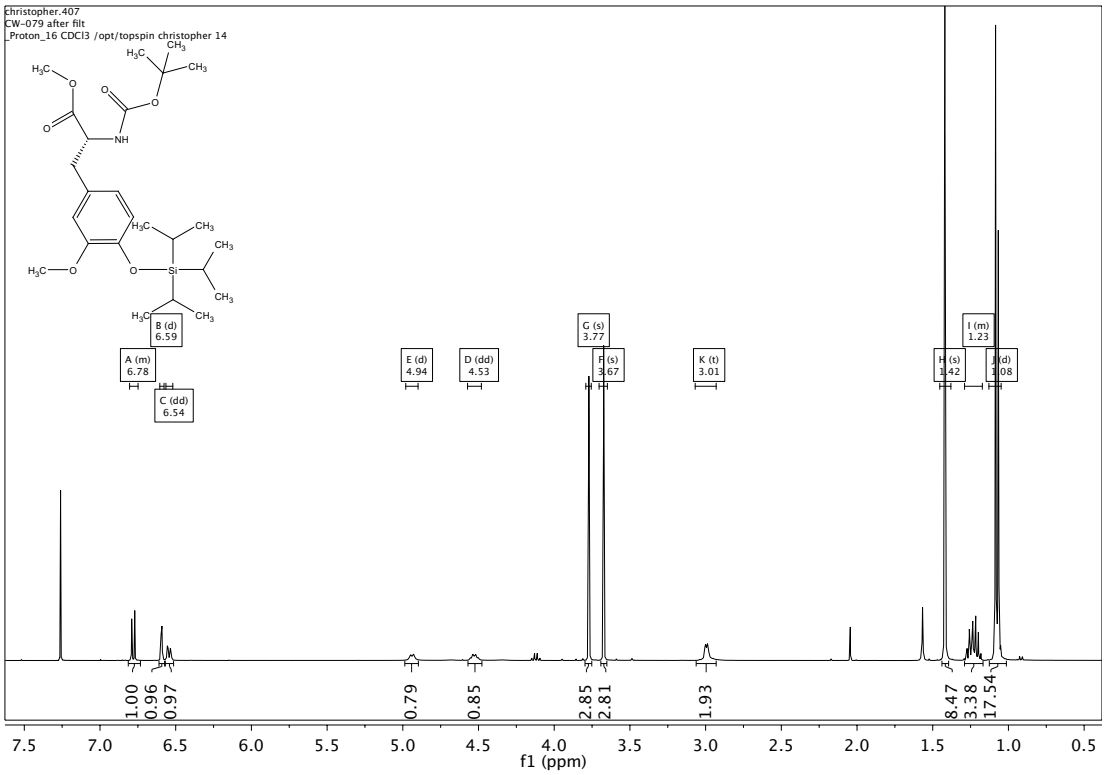
**Methyl-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(triisopropyl-silyl)oxy]-phenyl}propanoate (3.99):**



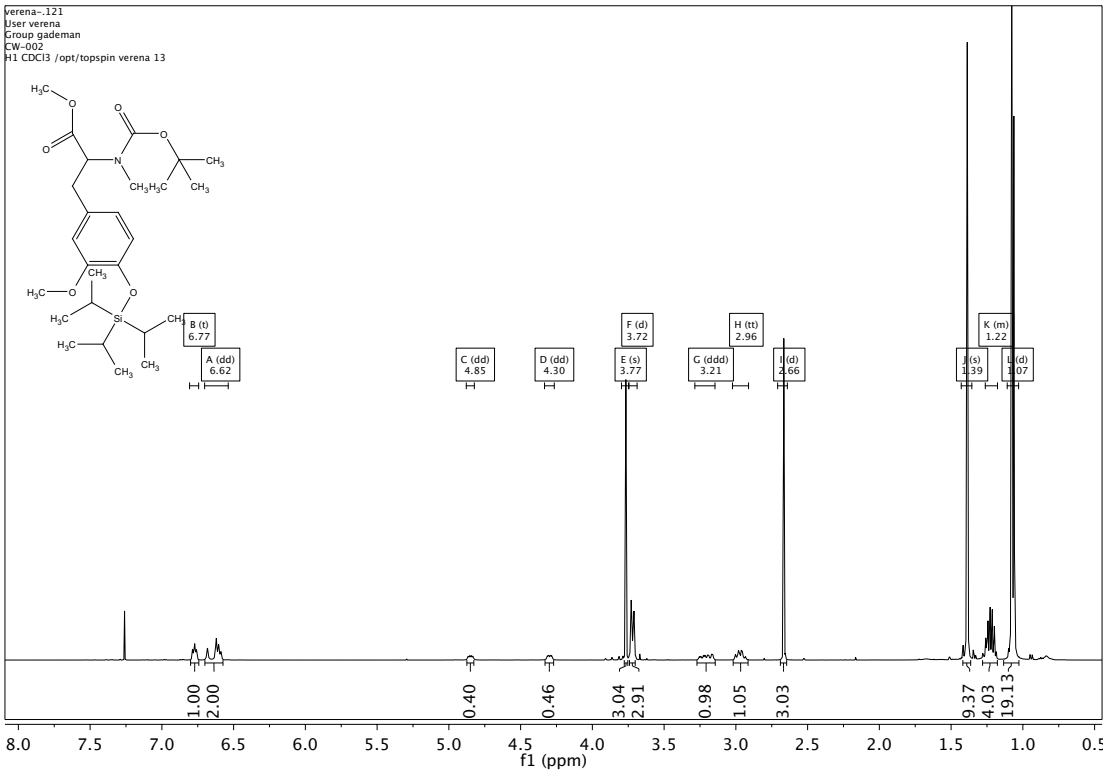



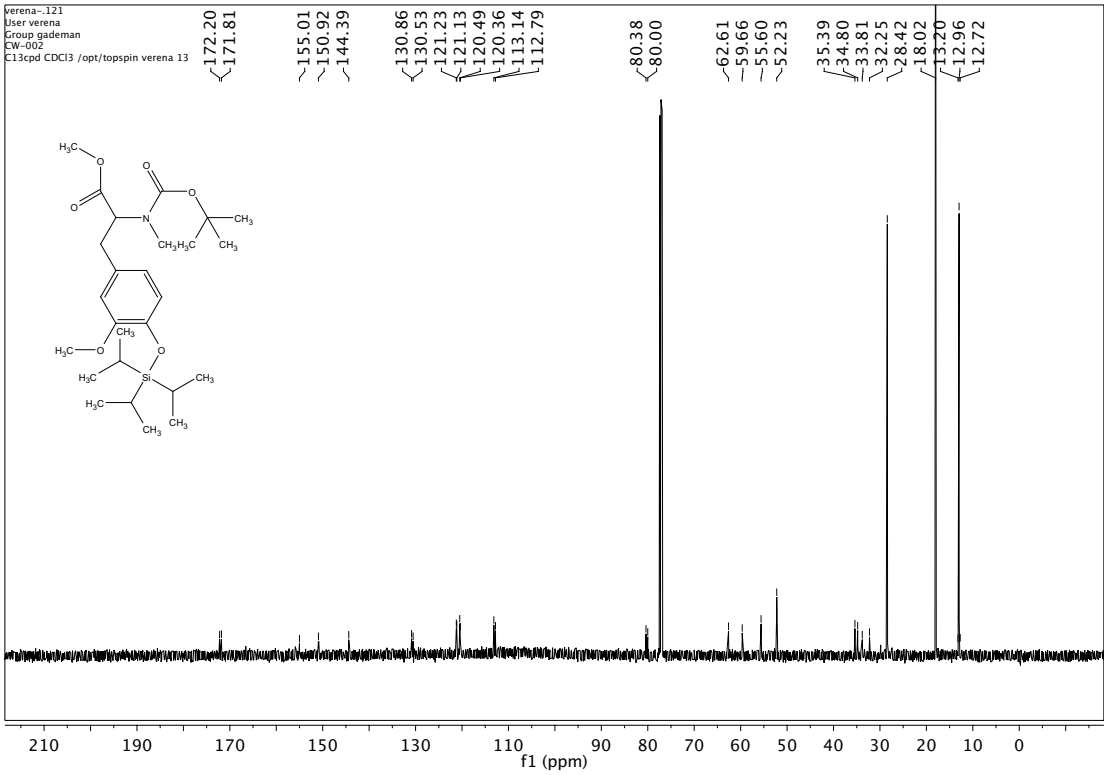
**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl} propanoate (3.100):**



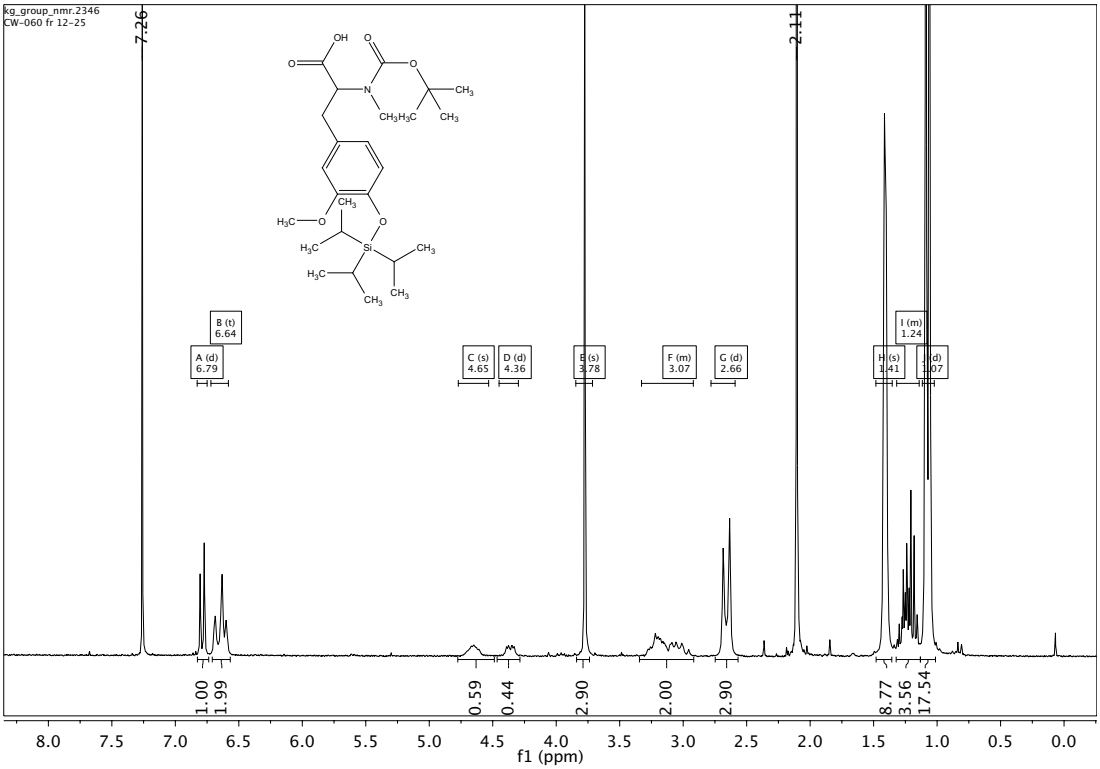



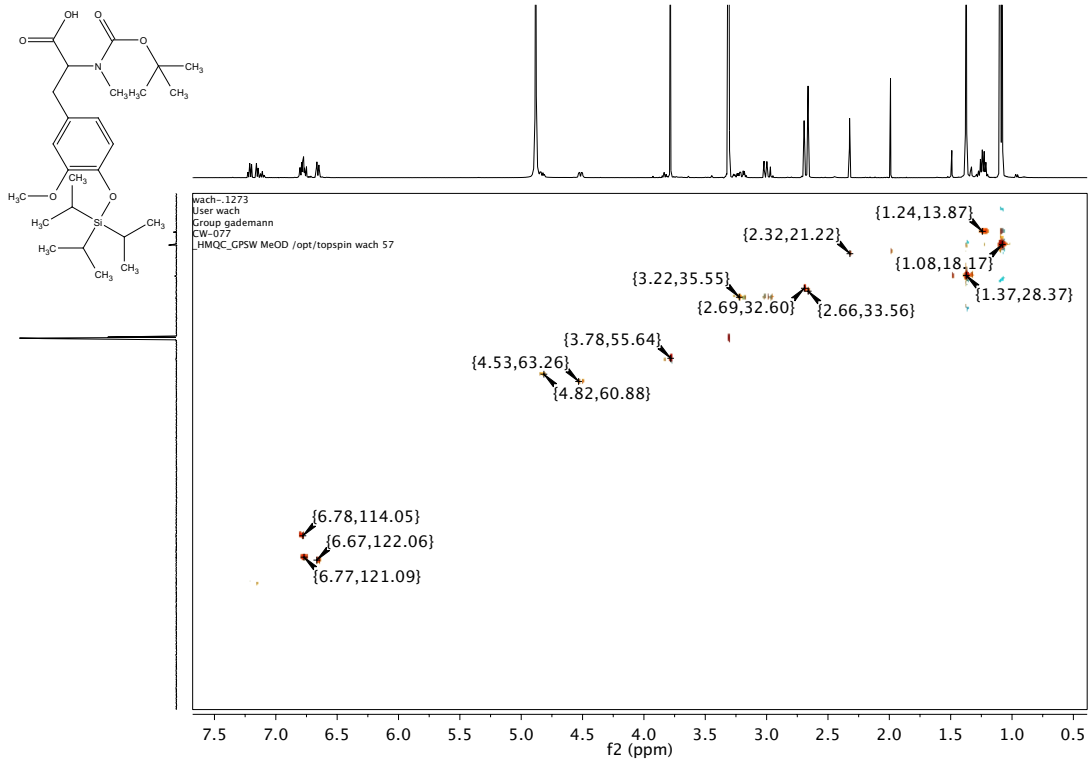
**Methyl-{[*tert*-butoxycarbonyl](methyl)amino}-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}propanoate (3.105):**

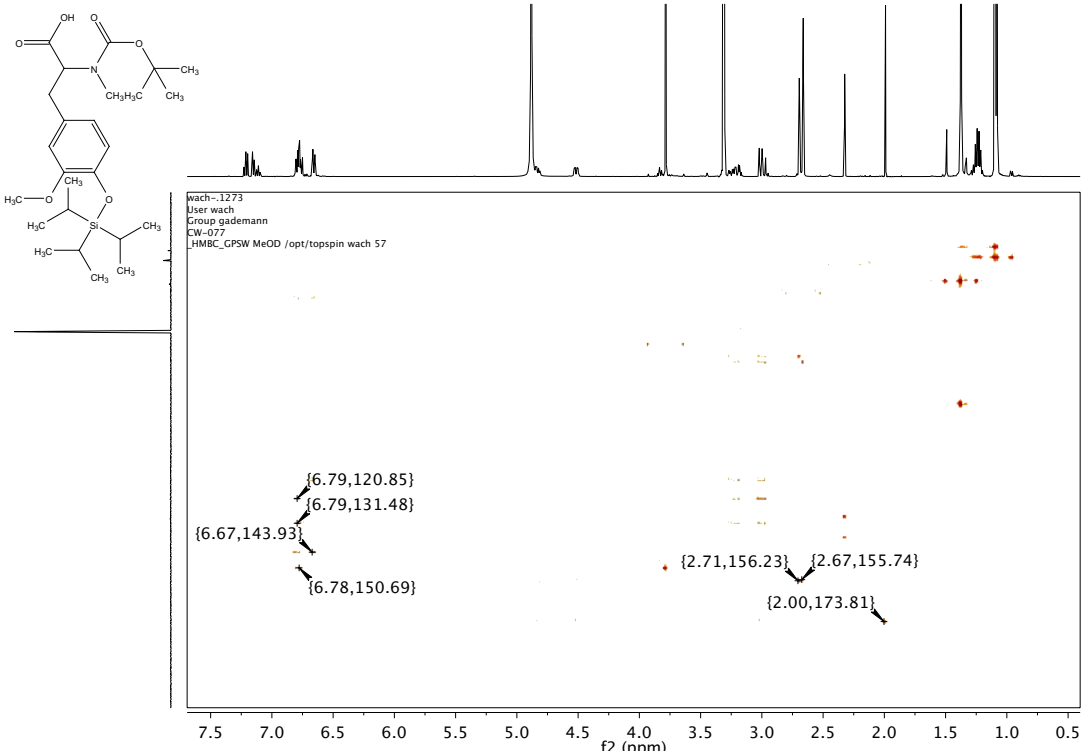


**2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}propanoic acid (3.106):**




wach--1273
User wach
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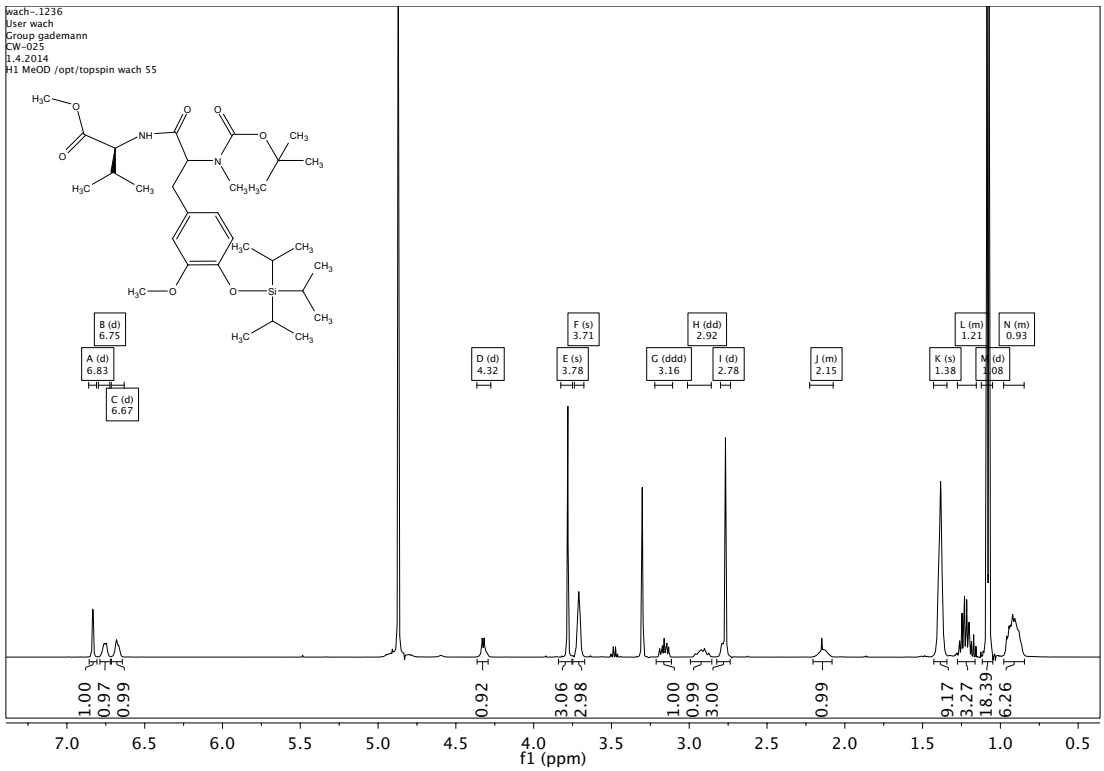
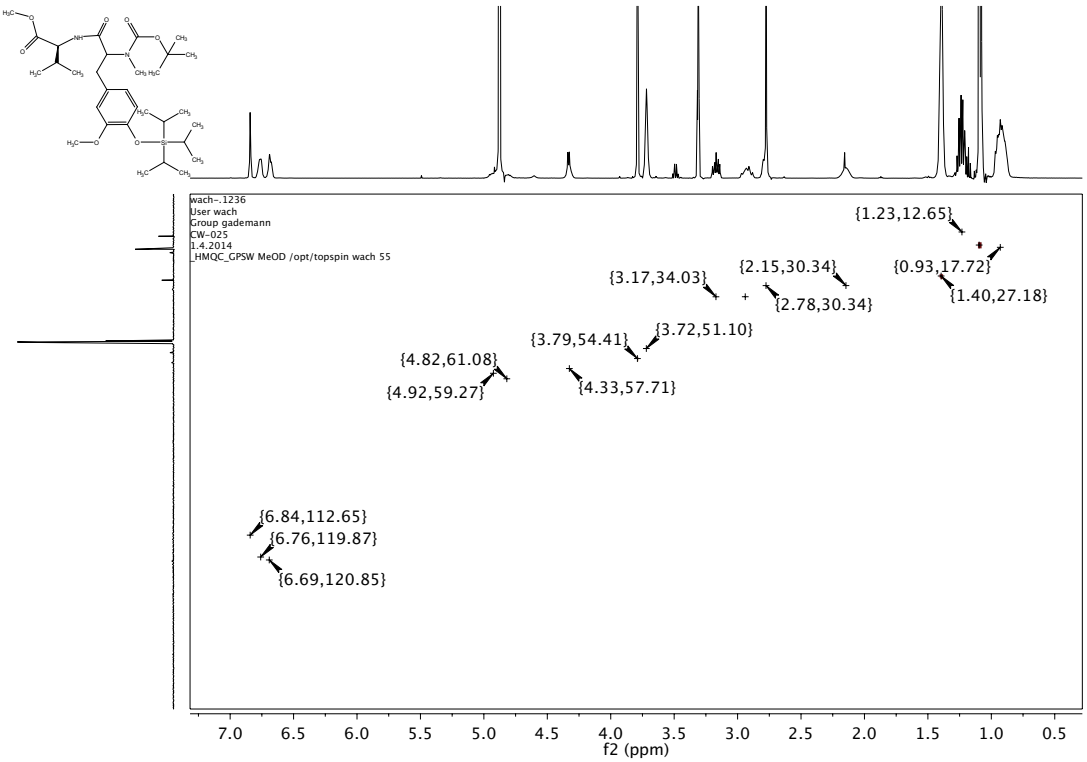
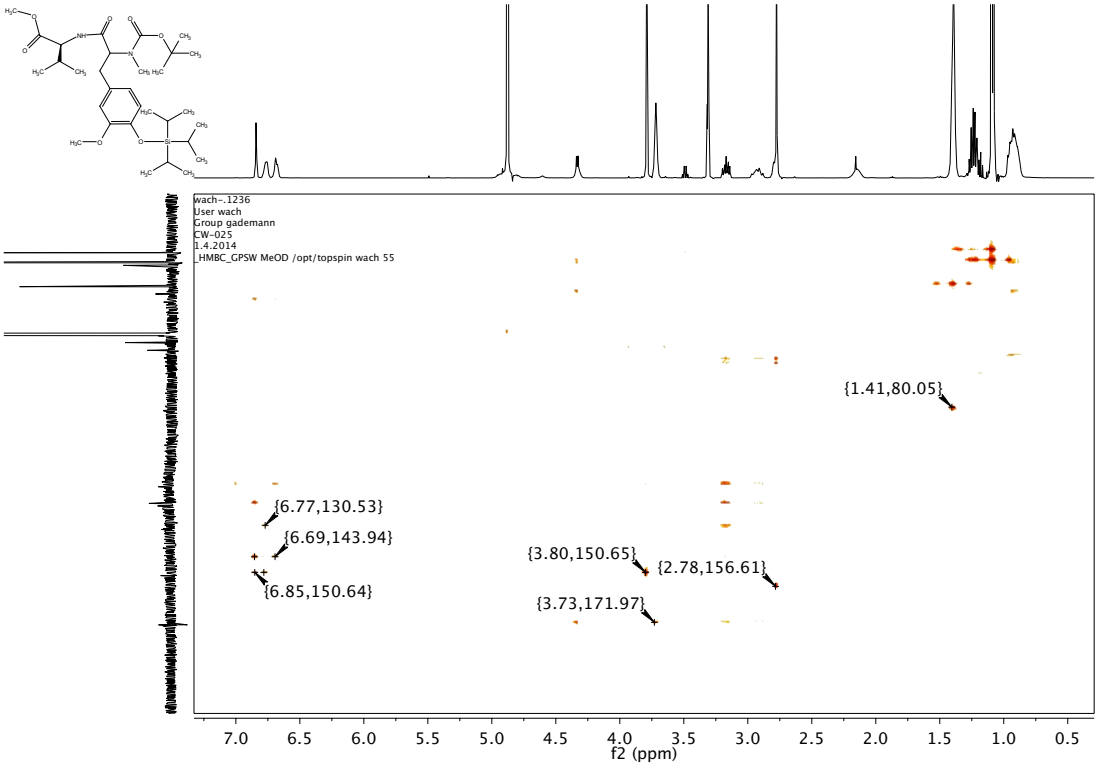
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

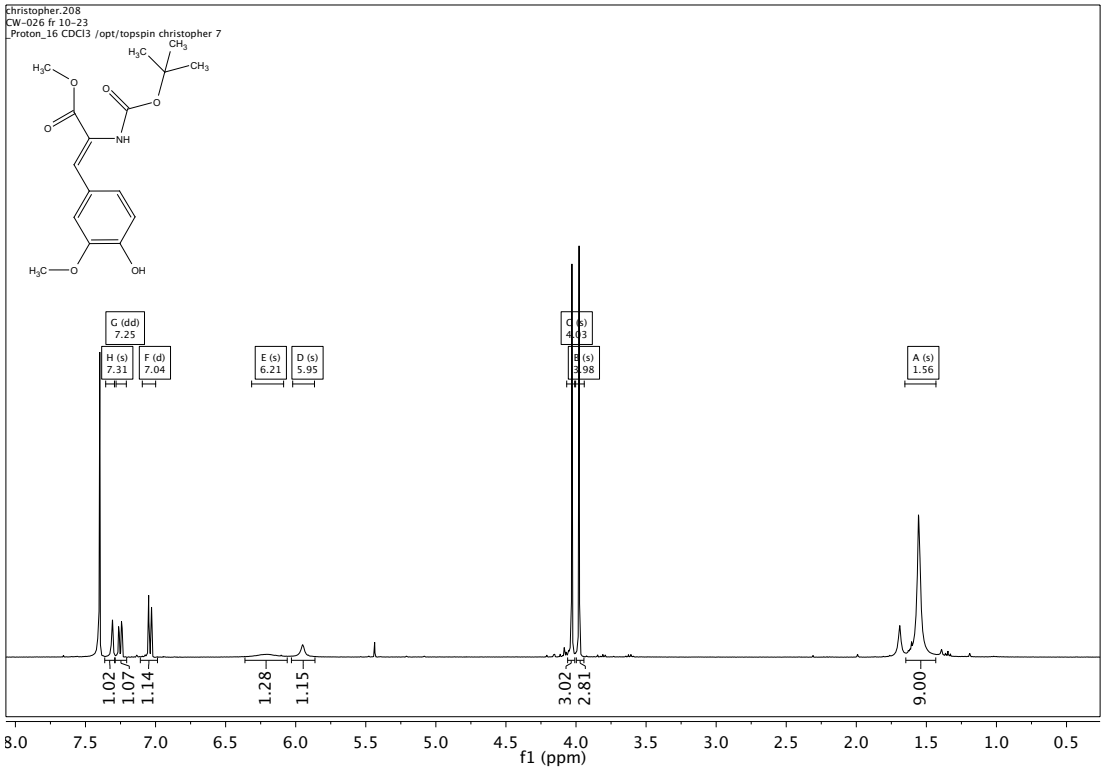
**Methyl {2-[(*tert*-butoxycarbonyl)methyl]amino-3-{3-methoxy-4-[(triisopropylsilyl)-oxy]phenyl}propanoyl}-*L*-valinate (3.107):**

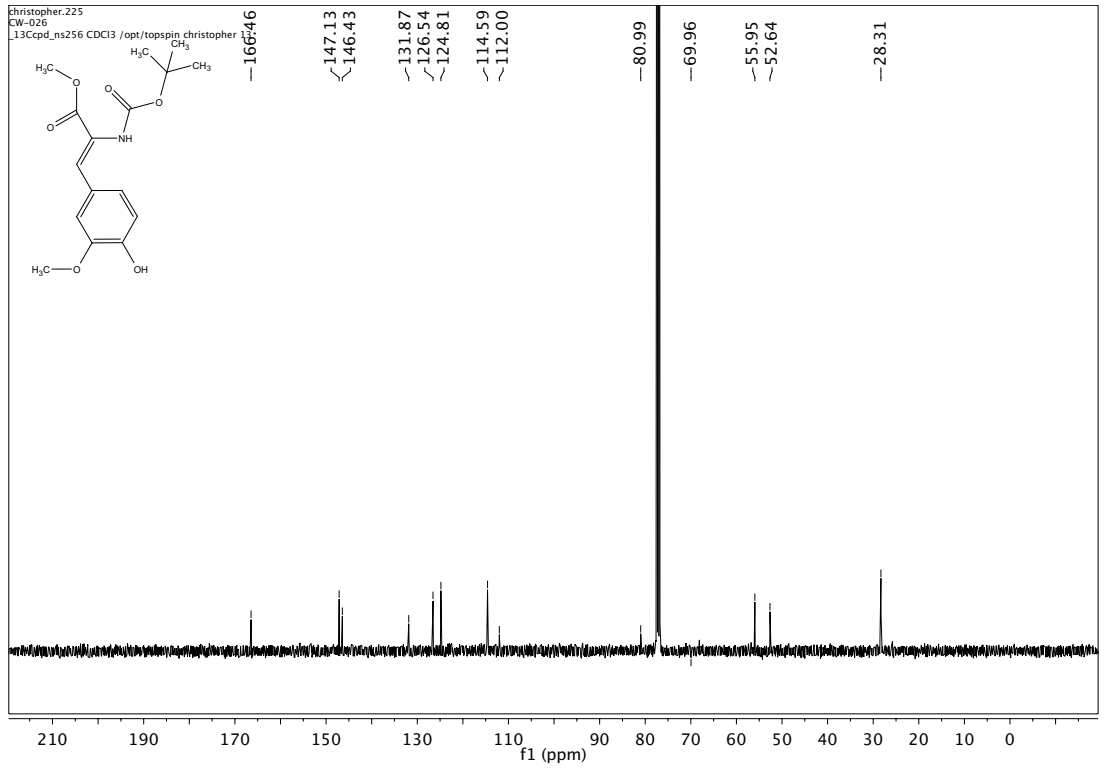


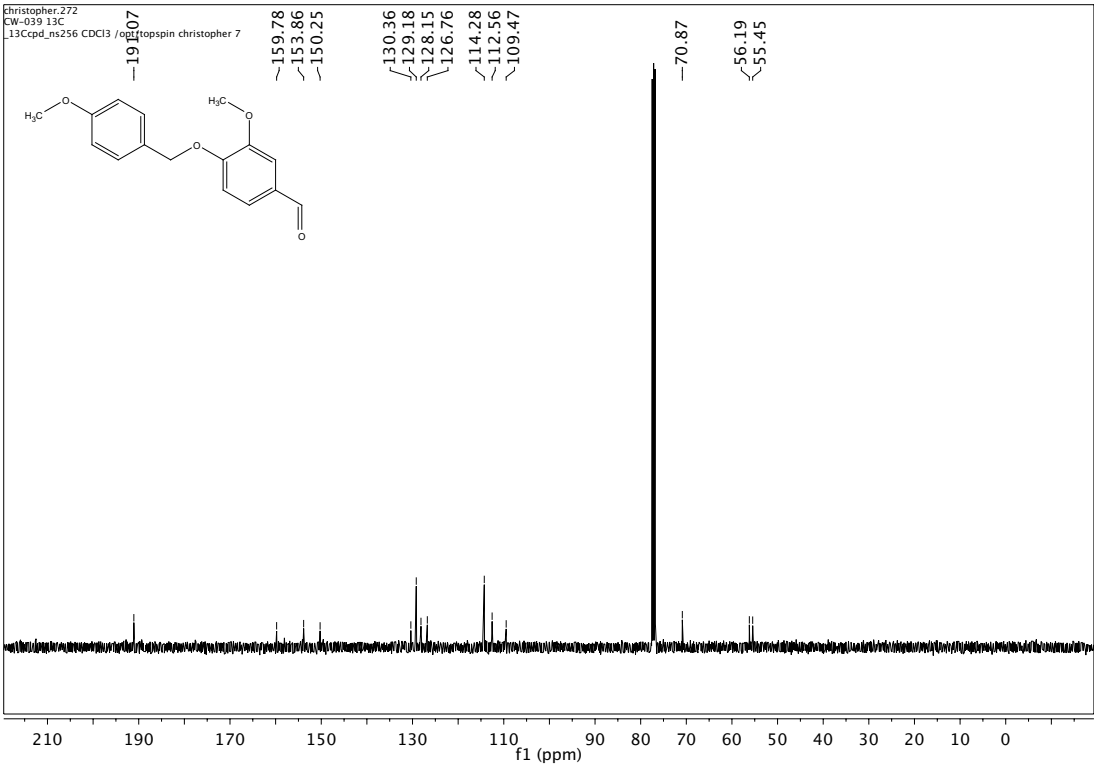

wach-.1236
User wach
Group gademann
CW-025
1.4.2014
_HMBC_GPSW MeOD /opt/topspin wach 55
{1.41,80.05}
{6.77,130.53}
{6.69,143.94}
{6.85,150.64}
{3.80,150.65}
{2.78,156.61}
{3.73,171.97}
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-hydroxy-3-methoxyphenyl)-acrylate (3.98):**

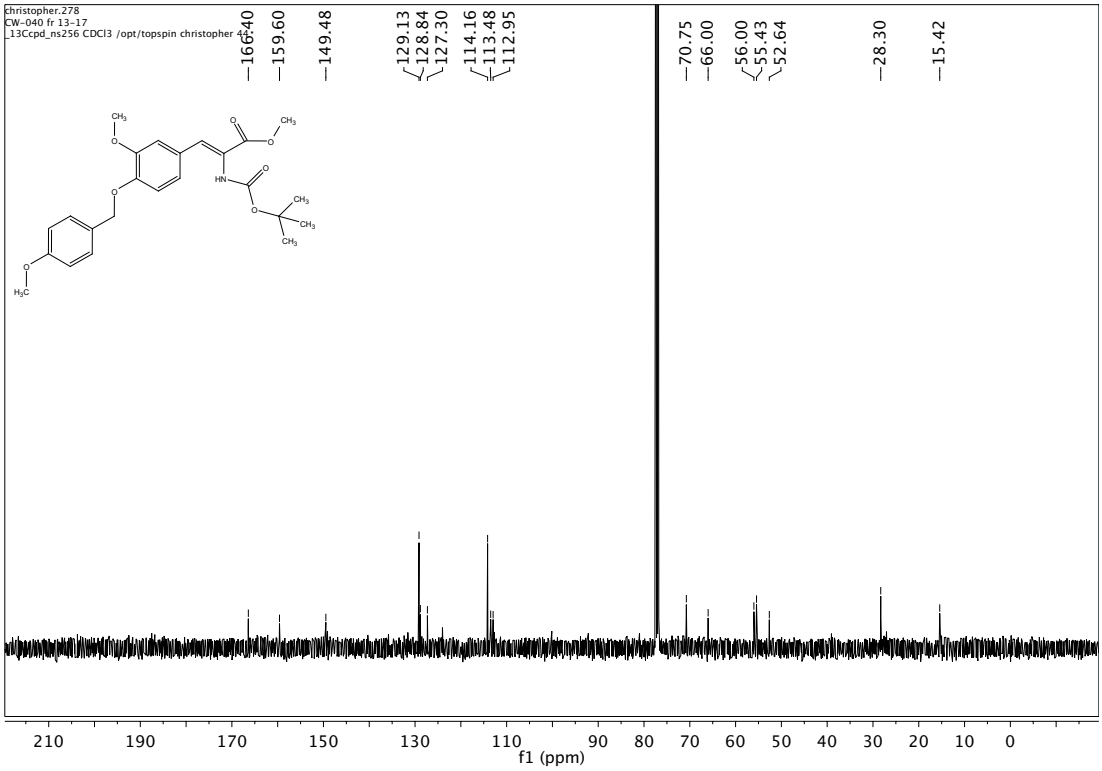


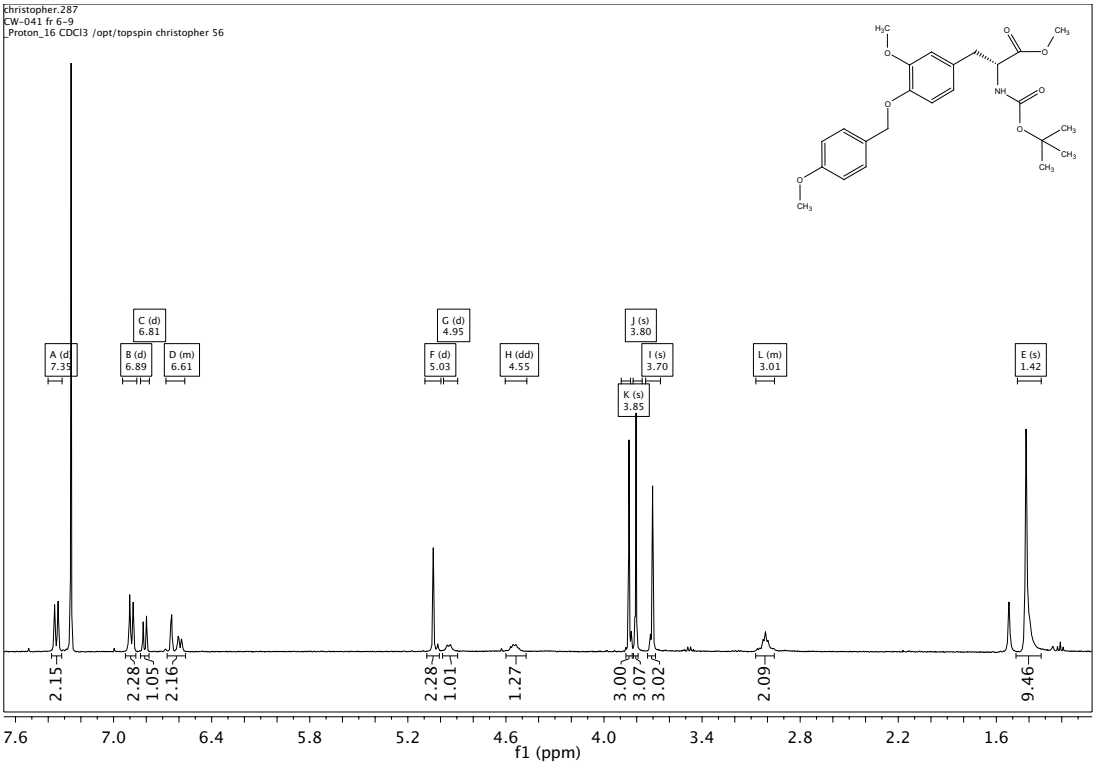
## 3-Methoxy-4-[(4-methoxybenzyl)oxy]benzaldehyde (S30):

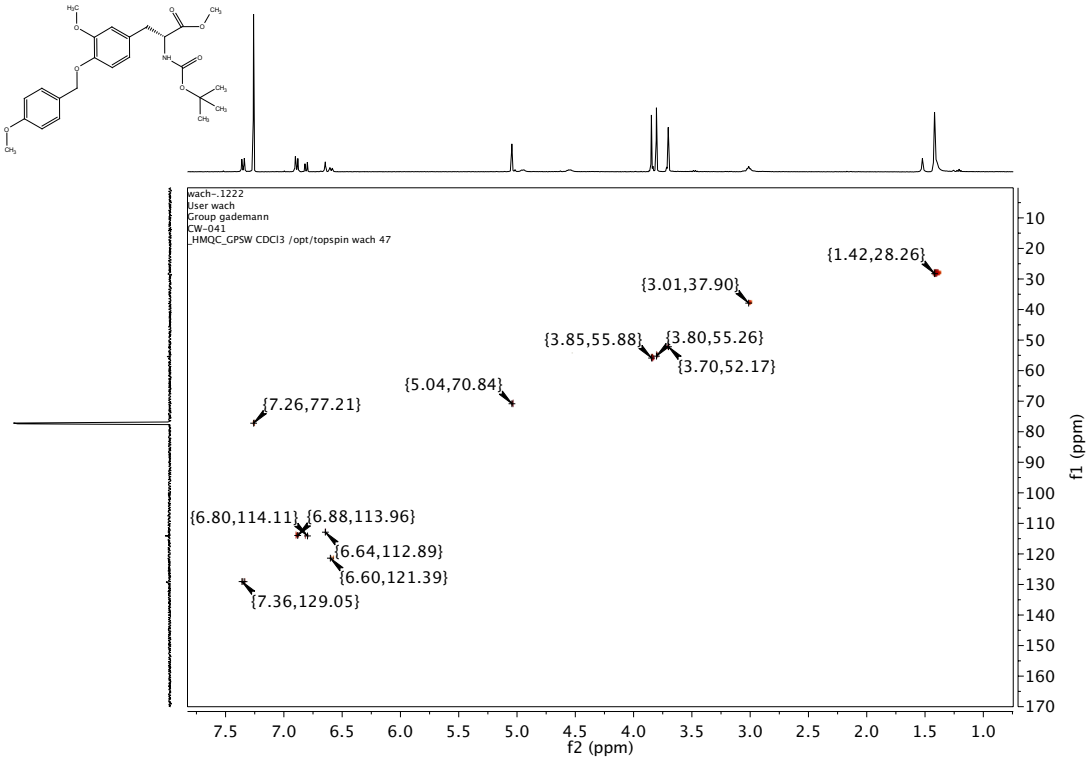


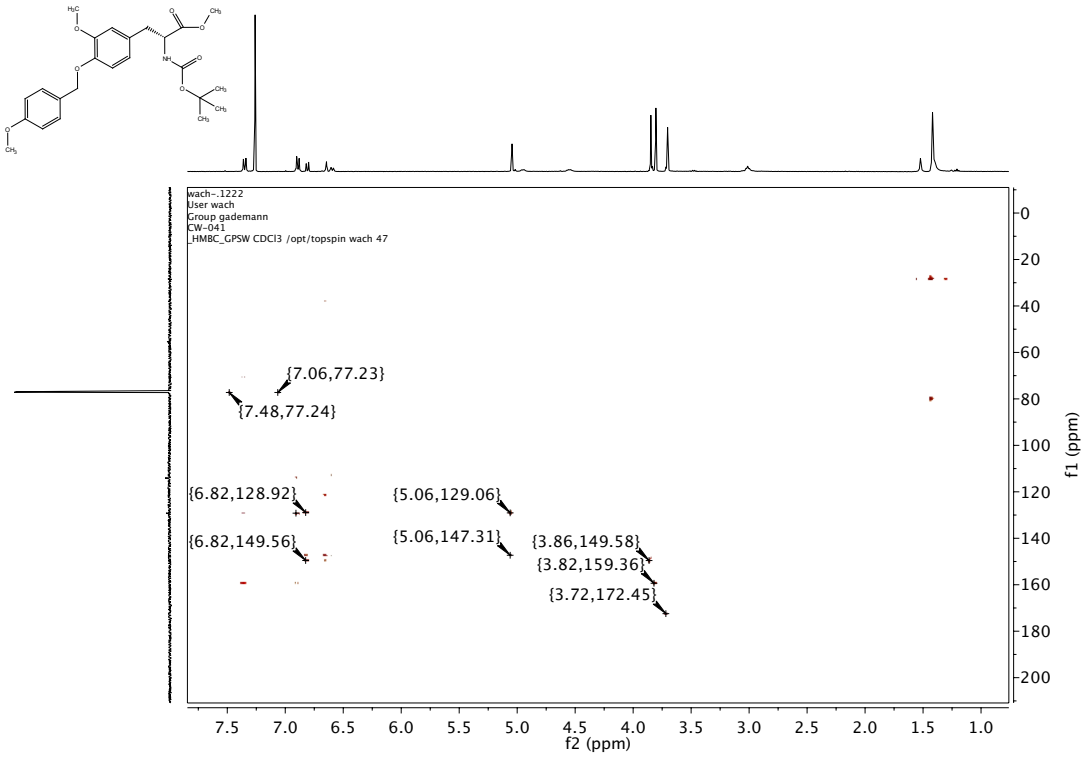
**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(4-methoxybenzyl)-oxy]phenyl}acrylate (S31):**



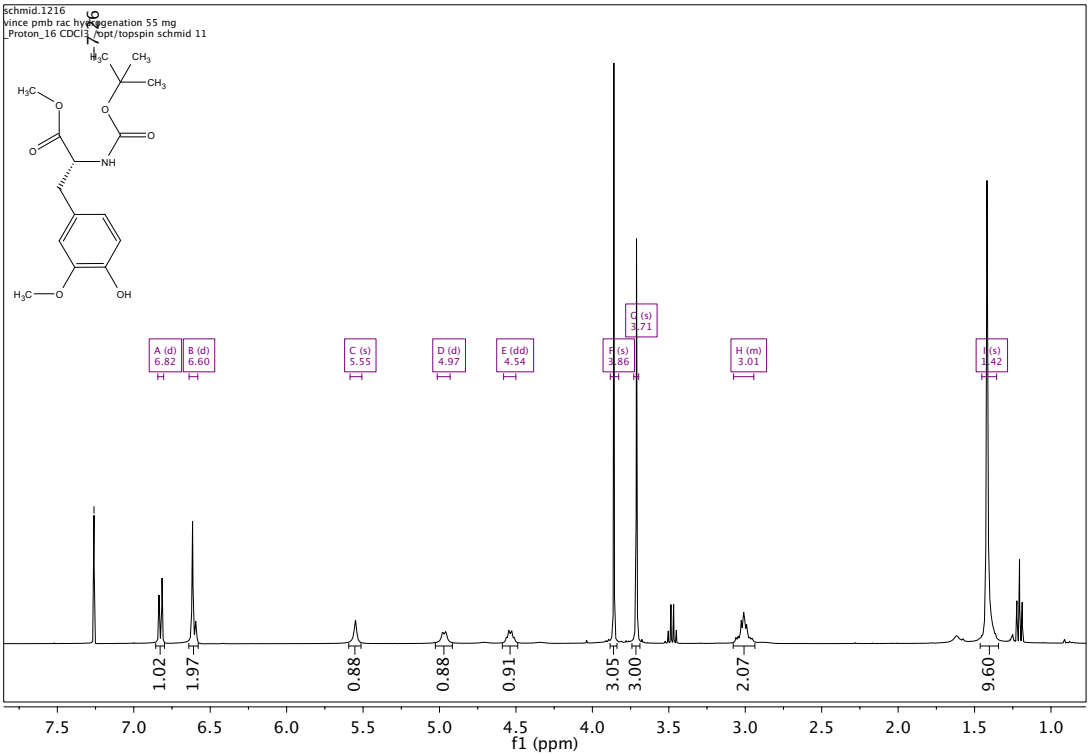
**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-{3-methoxy-4-[(4-methoxy-benzyl)-oxy]phenyl}propanoate (S32):**

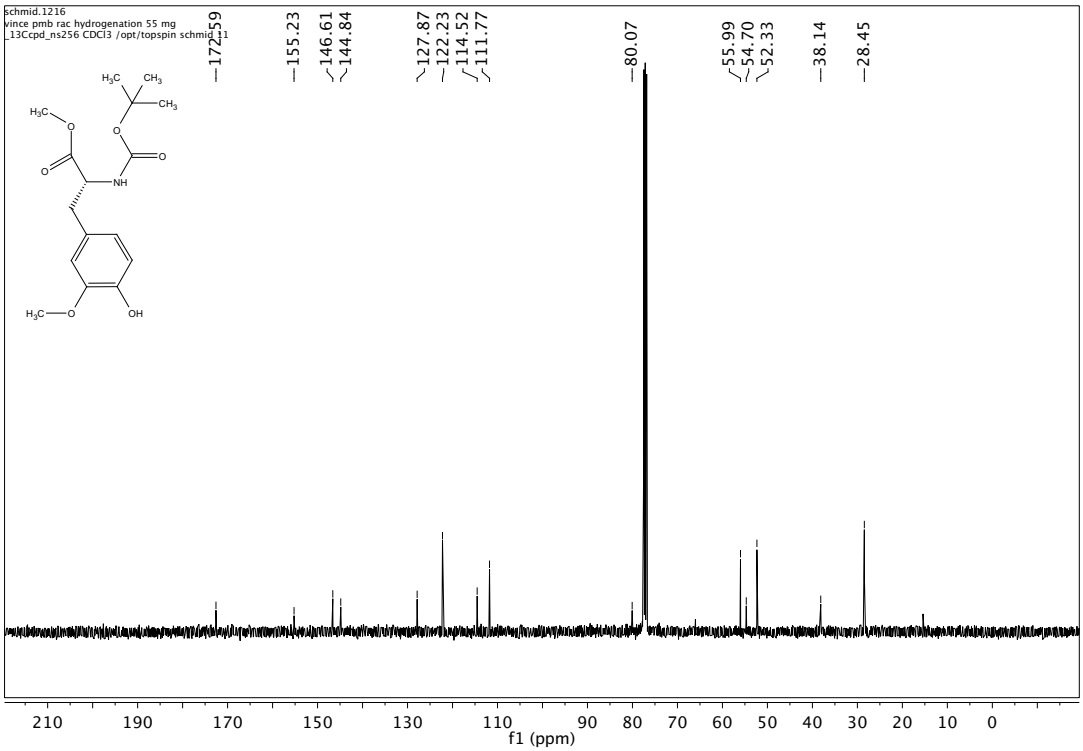


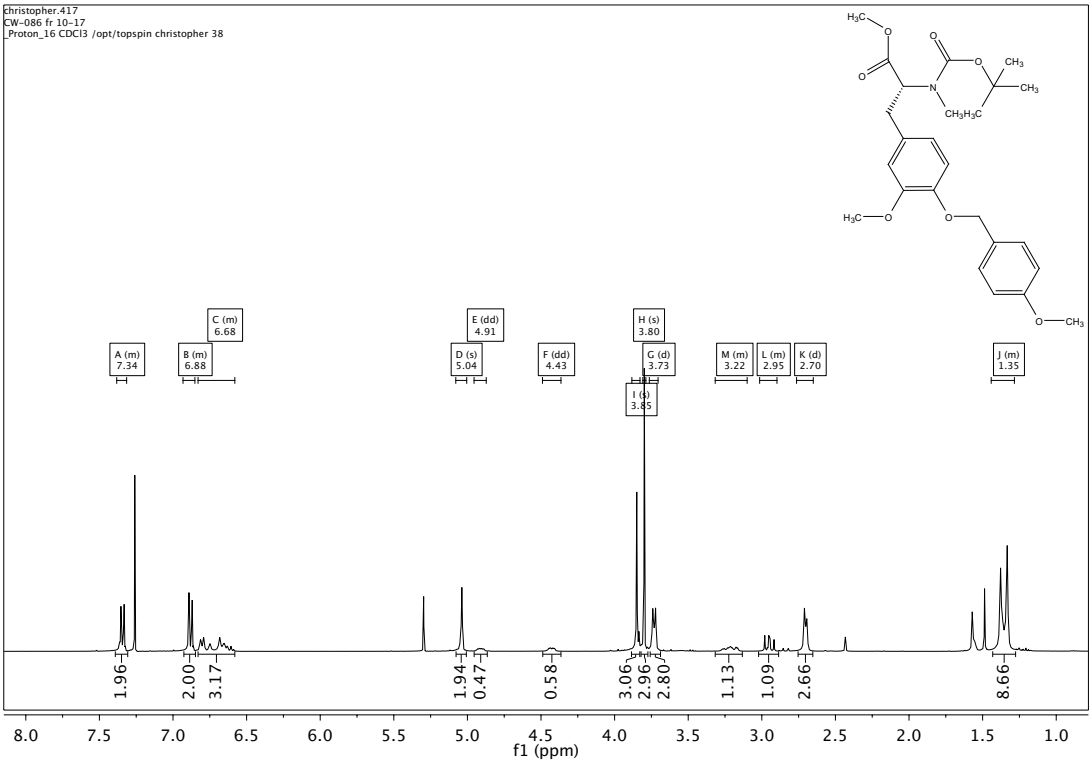

wach-.1222
User wach
Group gademann
CW-041
_HMBC_GPSW CDCl3 /opt/topspin wach 47
{7.06,77.23}
{7.48,77.24}
{6.82,128.92}
{5.06,129.06}
{6.82,149.56}
{5.06,147.31}
{3.86,149.58}
{3.82,159.36}
{3.72,172.45}
f2 (ppm)
f1 (ppm)

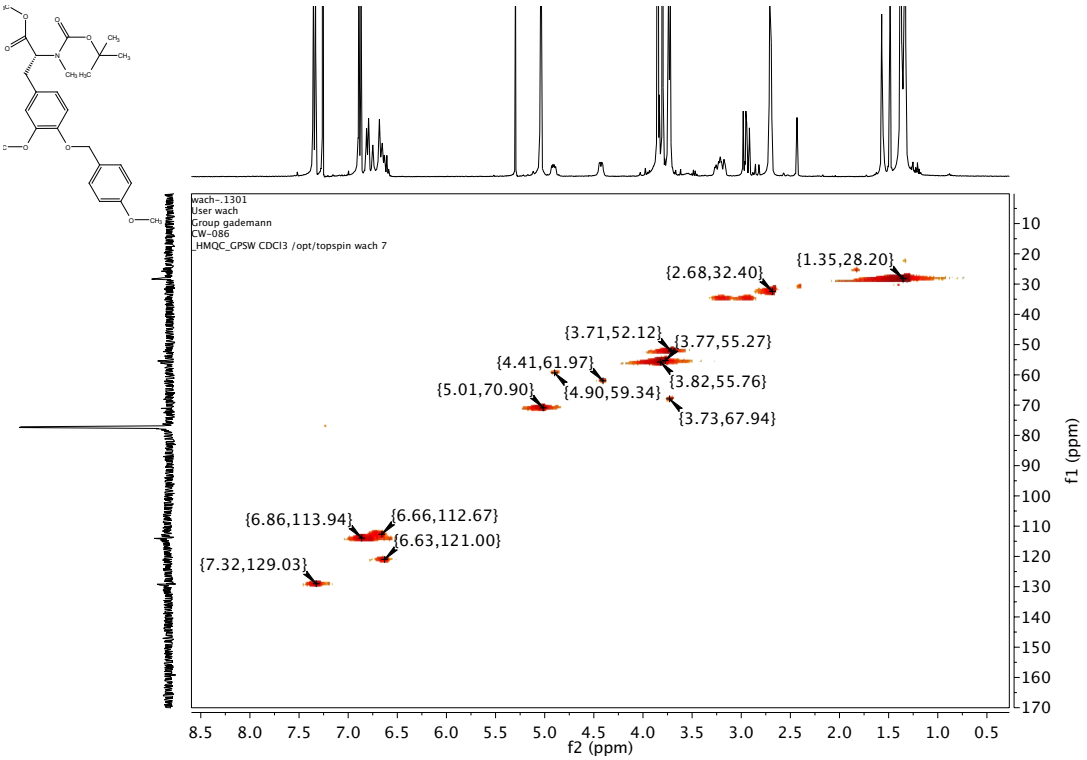
**Methyl (*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-hydroxy-3-methoxyphenyl)-propanoate (S33):**

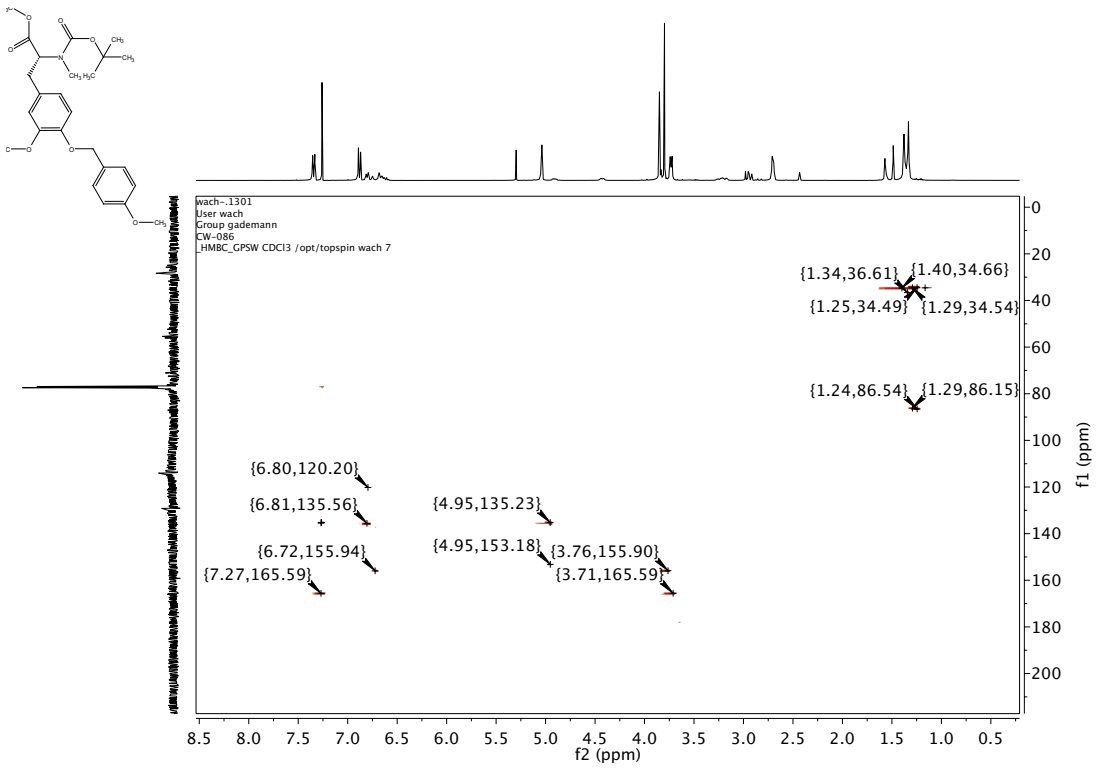


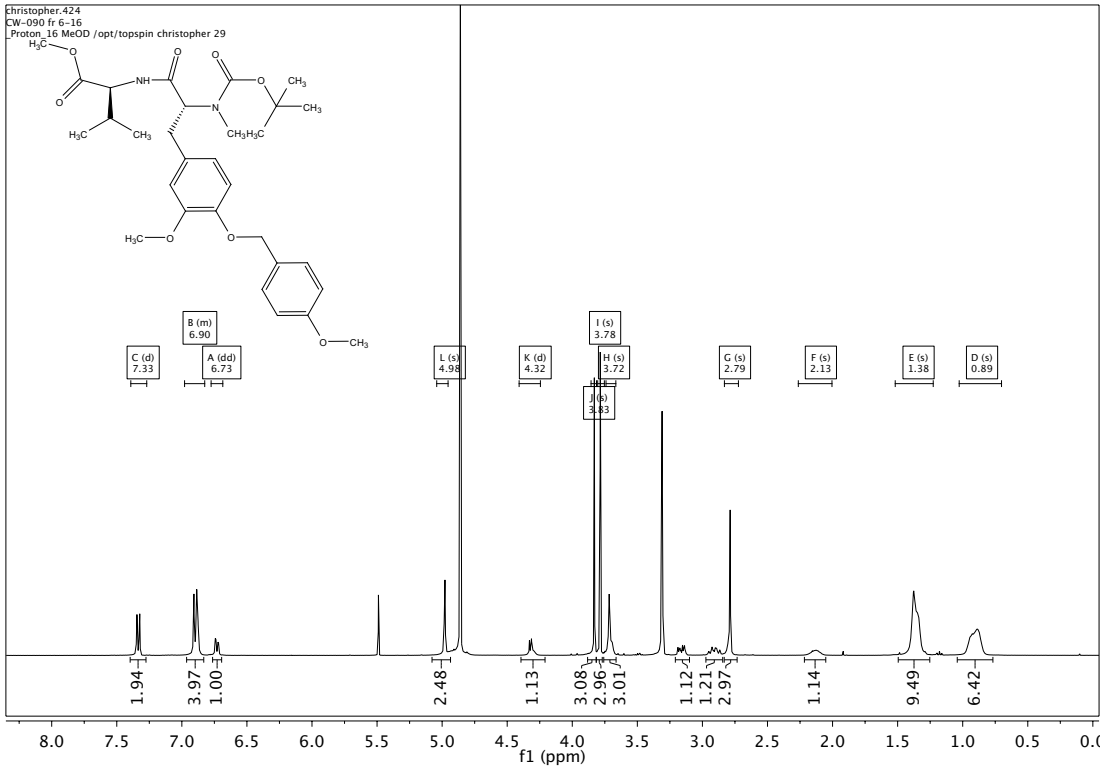
**Methyl (*rac*)-2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(4-methoxybenzyl)oxy]phenyl}propanoate (S34):**

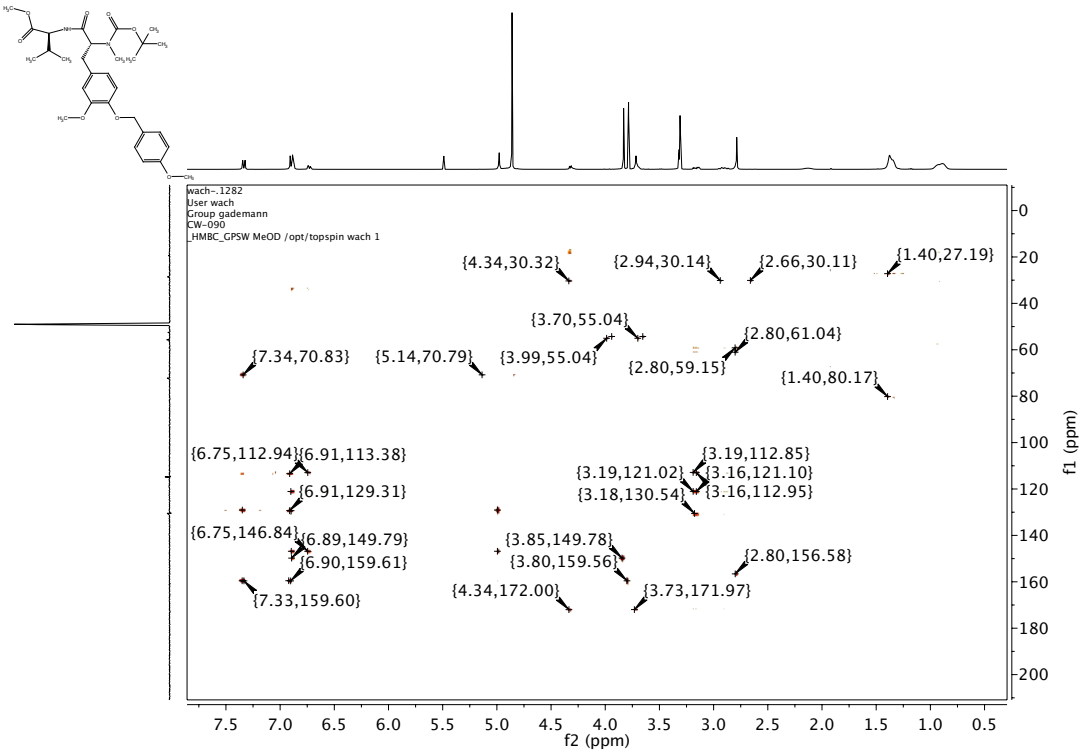


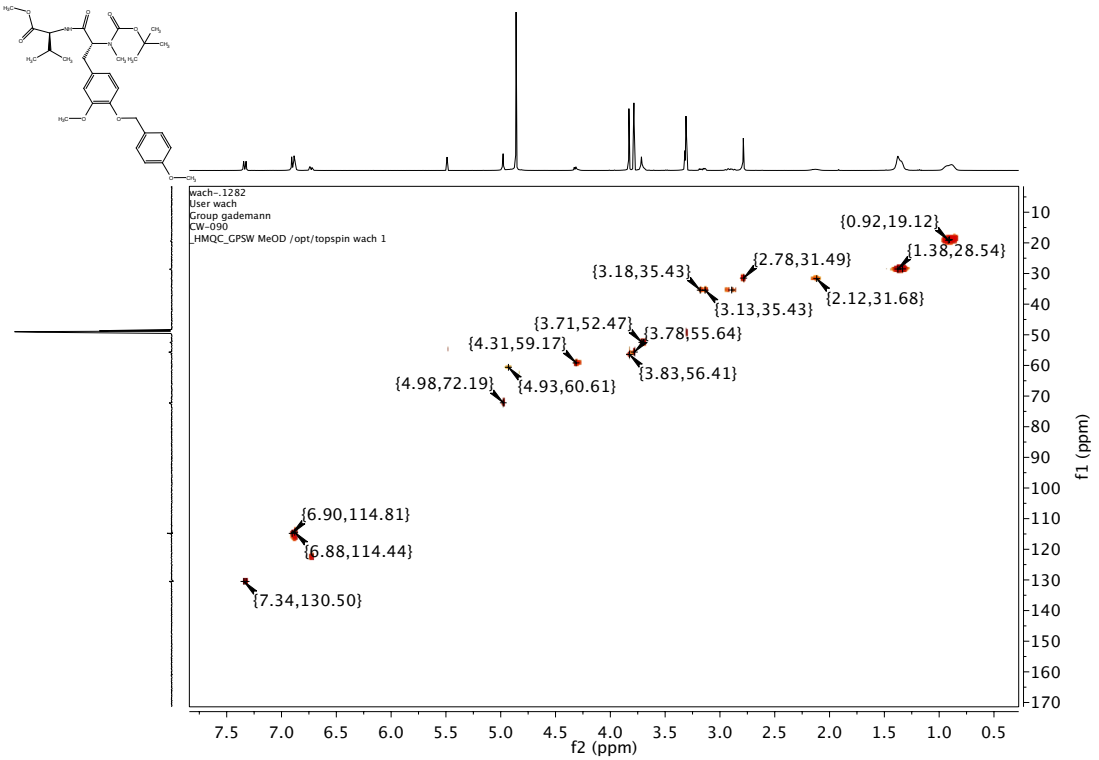




wach-.1301
User wach
Group gademann
CW-086
_HMBC_GPSW CDCl3 /opt/topspin wach 7
{1.34,36.61}
{1.40,34.66}
{1.25,34.49}
{1.29,34.54}
{1.24,86.54}
{1.29,86.15}
{6.80,120.20}
{6.81,135.56}
{4.95,135.23}
{6.72,155.94}
{4.95,153.18}
{3.76,155.90}
{7.27,165.59}
{3.71,165.59}
f2 (ppm)
f1 (ppm)

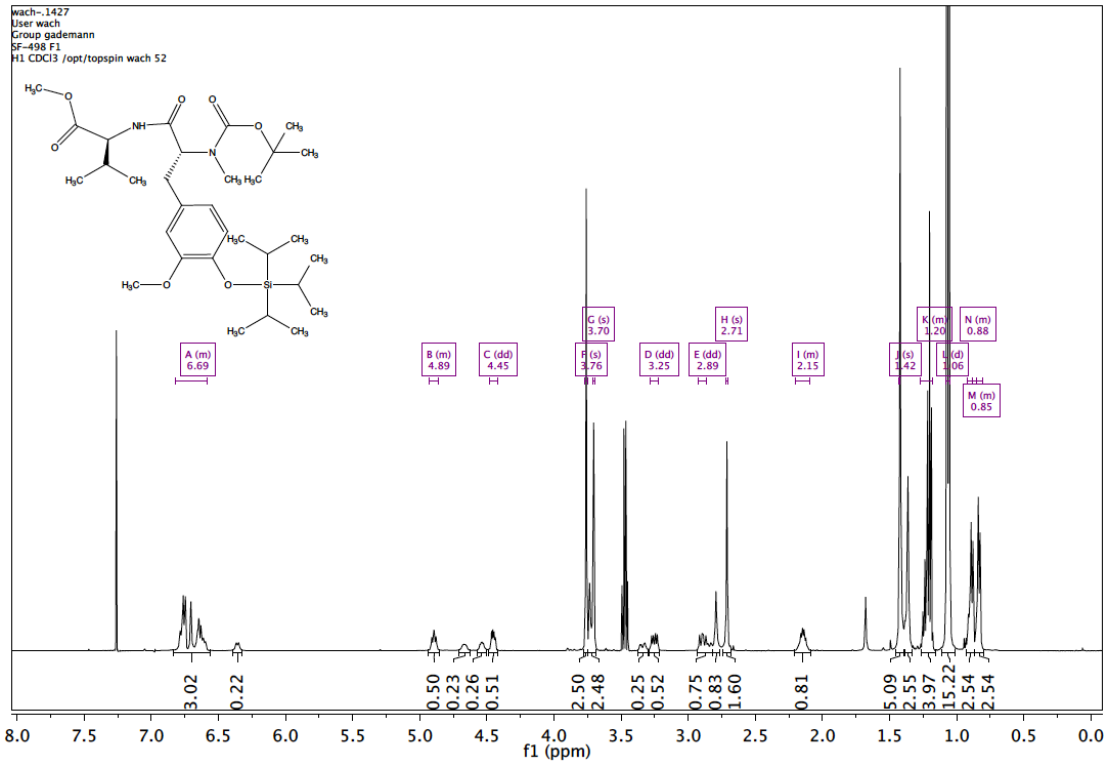
**Methyl (*rac*)-2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(4-methoxy-benzyl)oxy]phenyl}propanoyl-*L*-valinate (S35):**

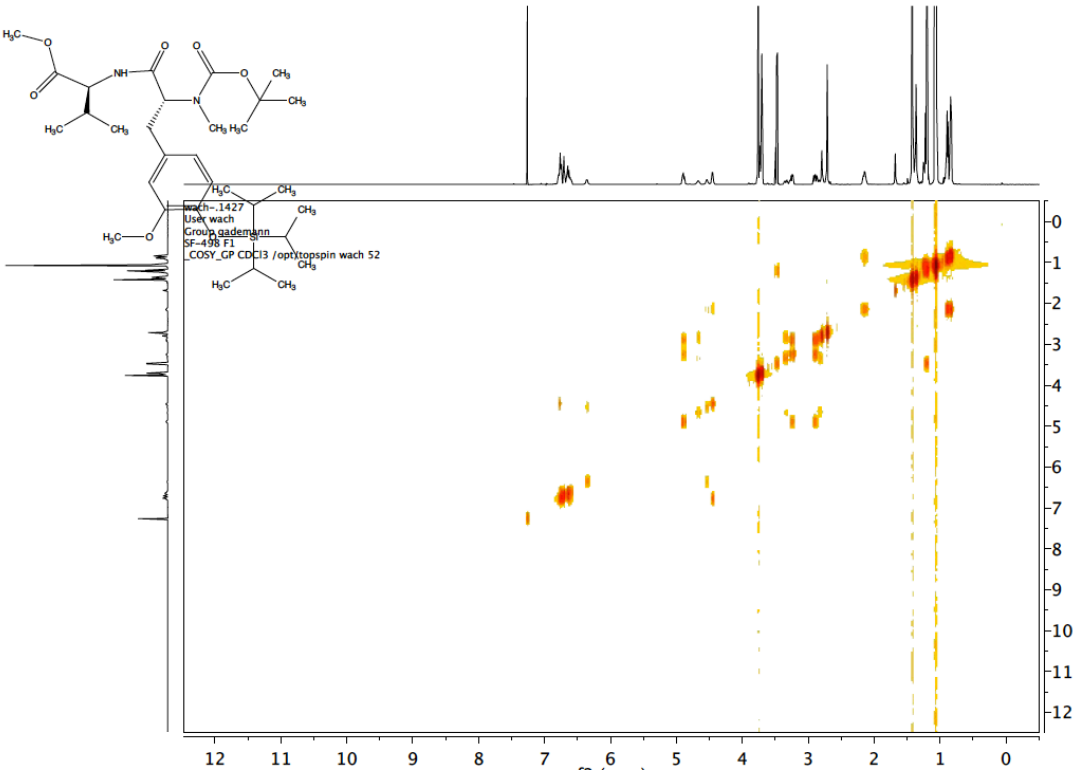


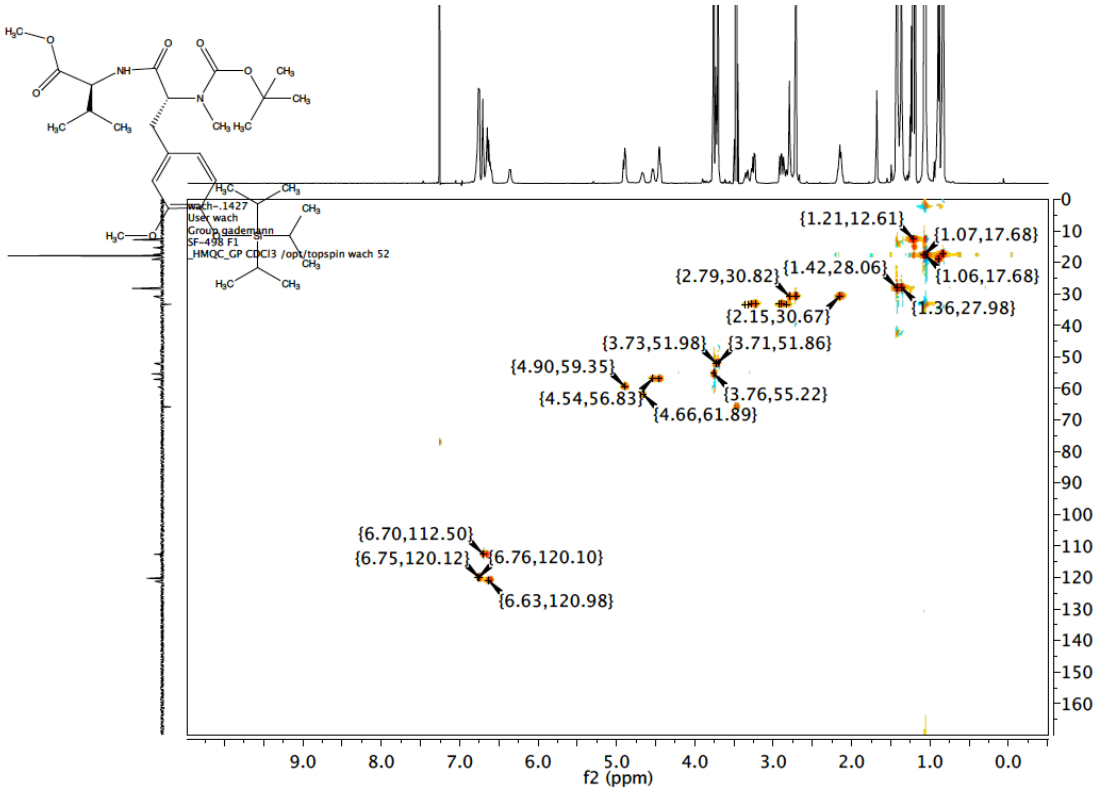



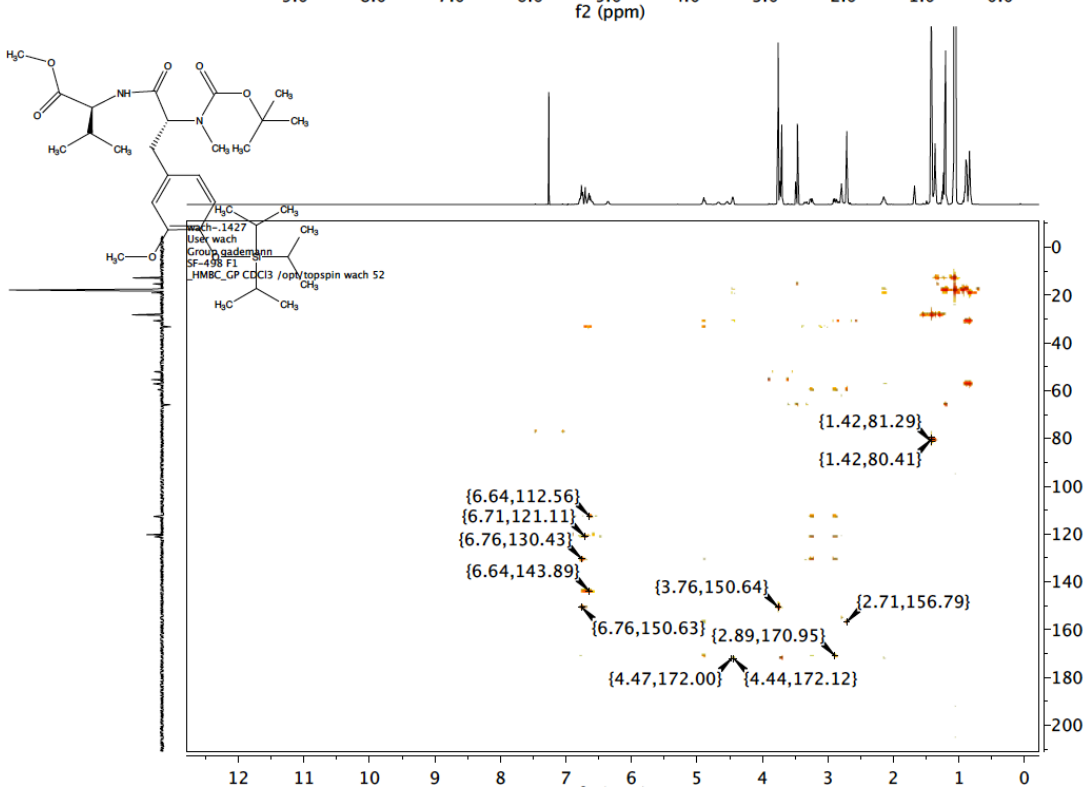

wach~_1282
User wach
Group gademann
CW-090
_HMQC_GPSW MeOD /opt/topspin wach 1
{0.92,19.12}
{1.38,28.54}
{2.78,31.49}
{3.18,35.43}
{3.13,35.43}
{2.12,31.68}
{3.71,52.47}
{3.78,55.64}
{4.31,59.17}
{3.83,56.41}
{4.98,72.19}
{4.93,60.61}
{6.90,114.81}
{6.88,114.44}
{7.34,130.50}
f2 (ppm)
f1 (ppm)

**Methyl [(*R*)-2-{[(benzyloxy)carbonyl](methyl)amino}-3-{3-methoxy-4-[(triiso-propylsilyl)oxy]phenyl}propanoyl}-*L*-valinate (S28):**

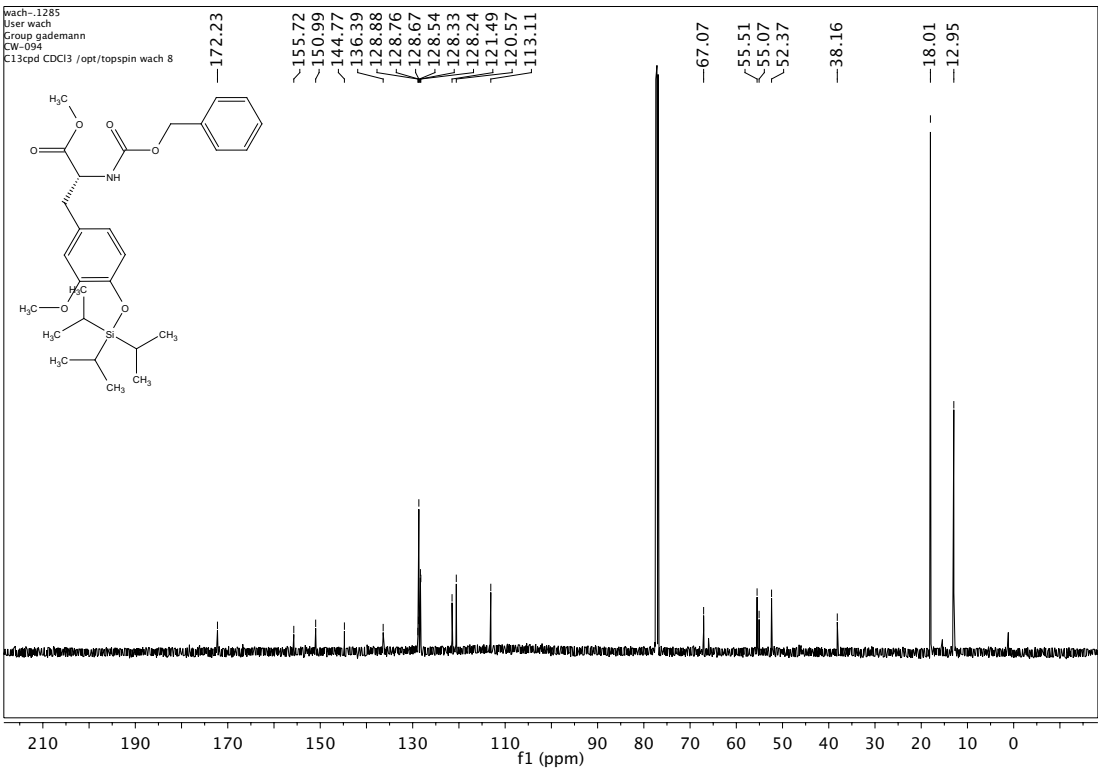


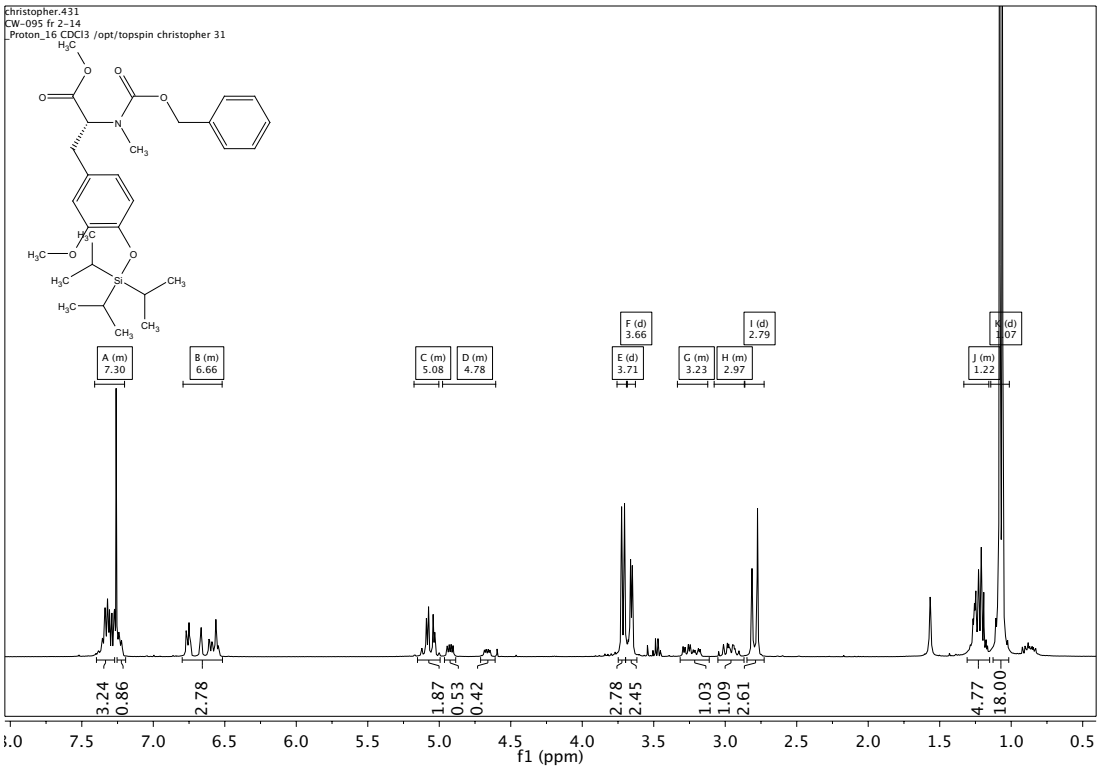

wach-.1427
User wach
Group gademann
SF-498 F1
_HMQC_GP CDCl3 /opt/topspin wach 52
{1.21,12.61}
{1.07,17.68}
{2.79,30.82}
{1.42,28.06}
{1.06,17.68}
{2.15,30.67}
{1.36,27.98}
{3.73,51.98}
{3.71,51.86}
{4.90,59.35}
{4.54,56.83}
{3.76,55.22}
{4.66,61.89}
{6.70,112.50}
{6.75,120.12}
{6.76,120.10}
{6.63,120.98}
f2 (ppm)

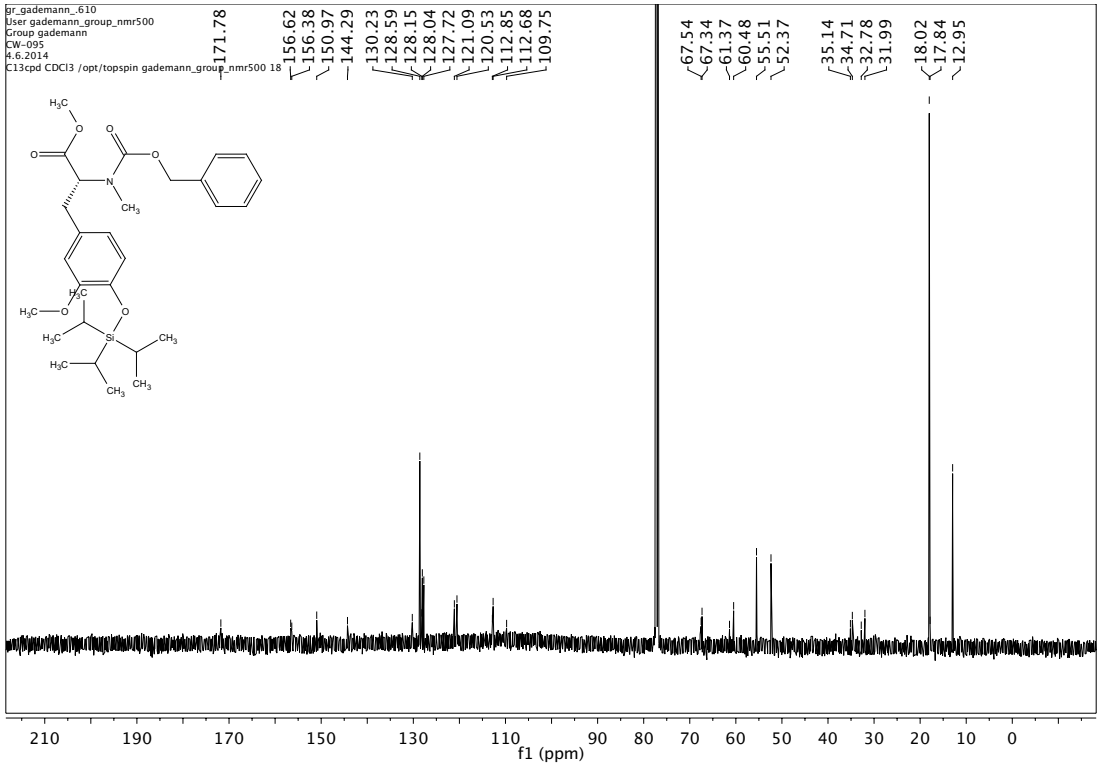

wach-.1427
User wach
Group gademann
SF-498 F1
_HMBC_GP CDCl3 /opt/topspin wach 52
{1.42,81.29}
{1.42,80.41}
{6.64,112.56}
{6.71,121.11}
{6.76,130.43}
{6.64,143.89}
{3.76,150.64}
{2.71,156.79}
{6.76,150.63}
{2.89,170.95}
{4.47,172.00}
{4.44,172.12}

**Methyl (*rac*)-2-{[(benzyloxy)carbonyl]amino}-3-{3-methoxy-4-[(triisopropyl-silyl)-oxy]phenyl}propanoate (3.109):**

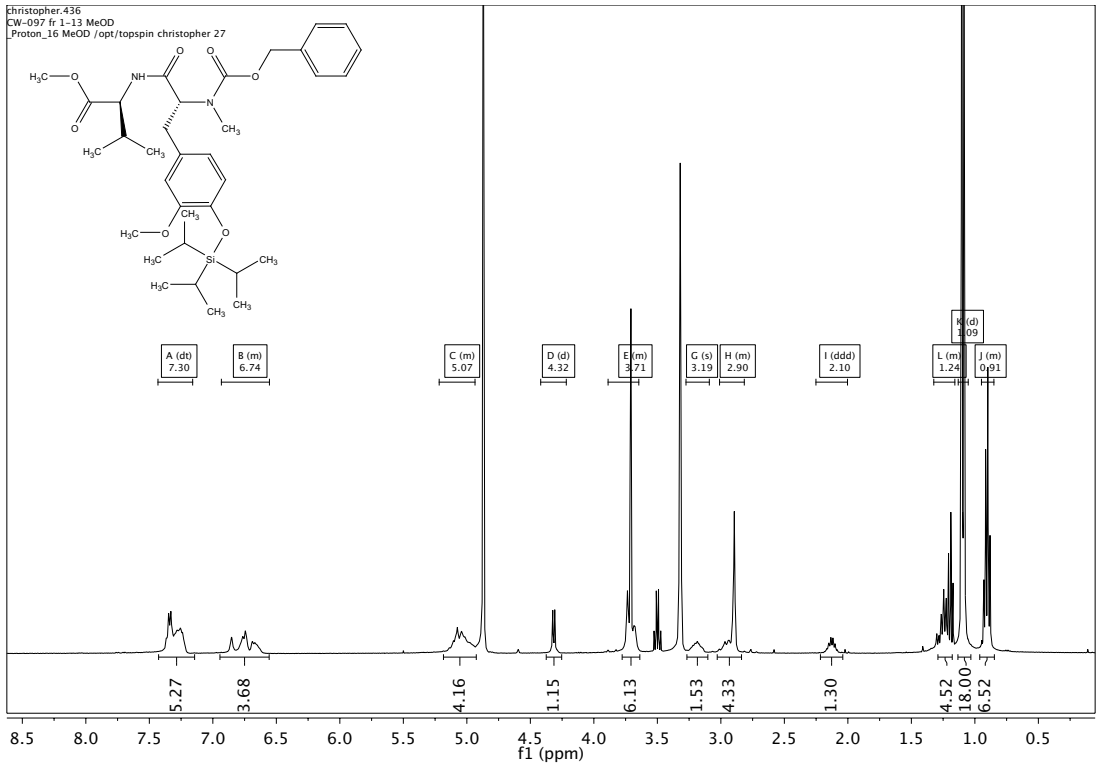


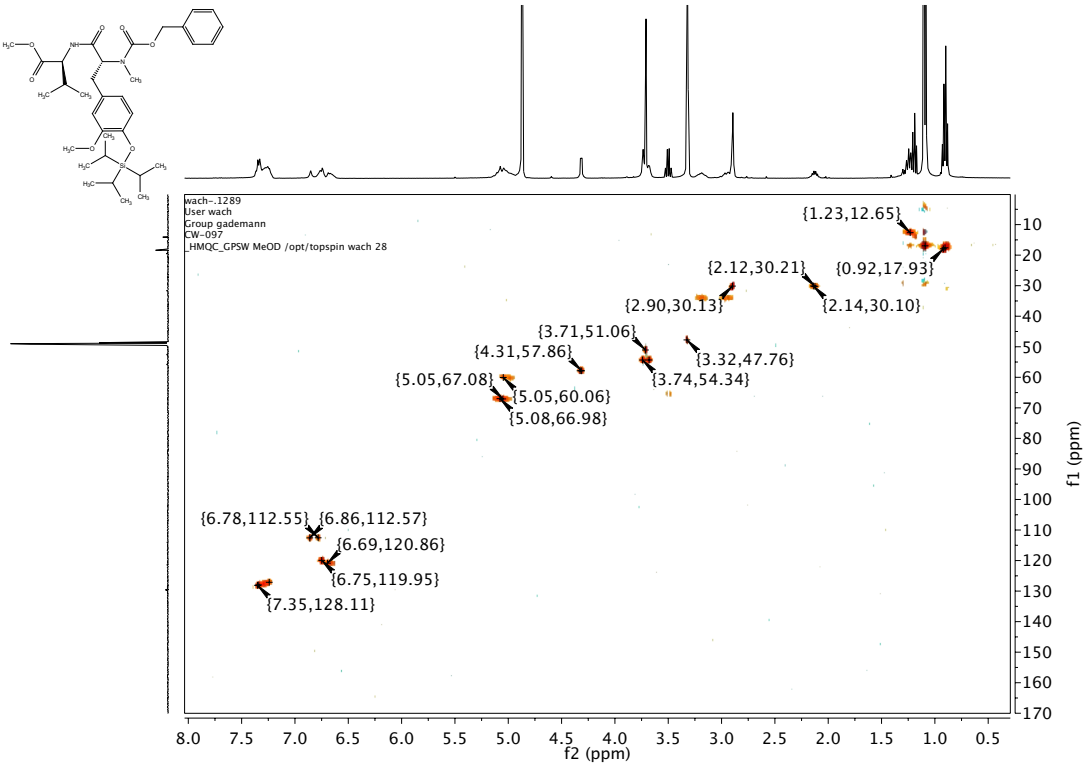
**Methyl (*rac*)-2-{[(benzyloxy)carbonyl](methyl)amino}-3-{3-methoxy-4-[(triisopropyl-silyl)oxy]phenyl}propanoate (S36):**

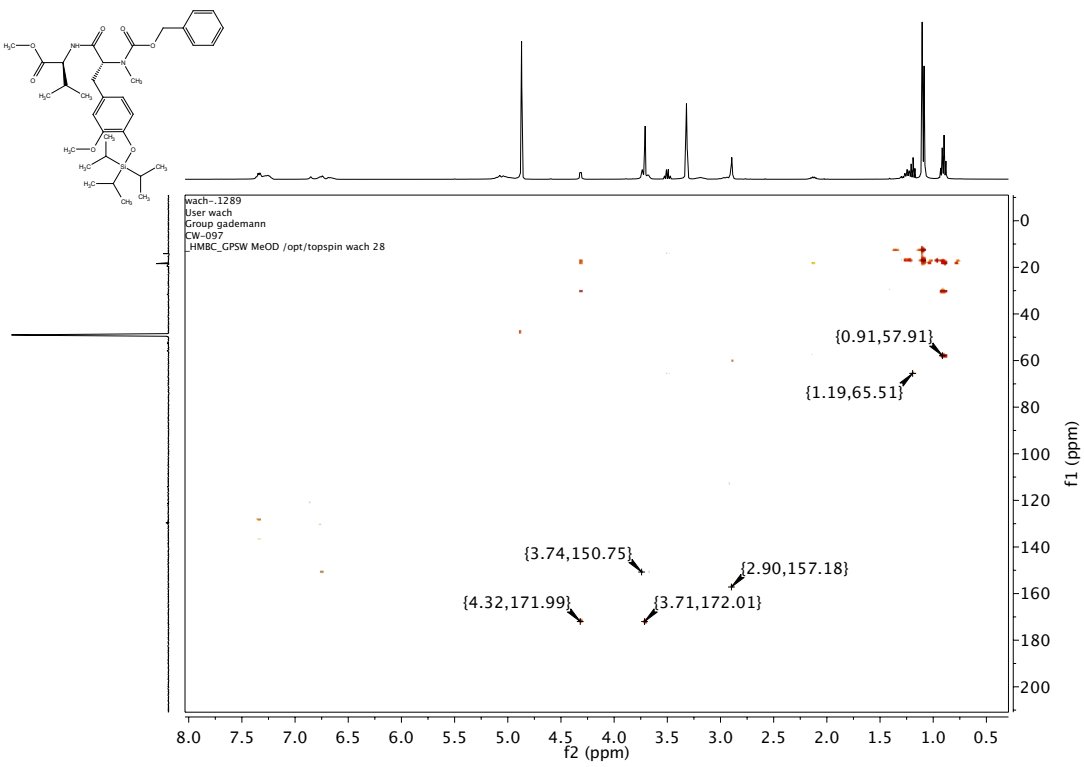


**Methyl [(*rac*)-2-{[(benzyloxy)carbonyl](methyl)amino}-3-{3-methoxy-4-[(triisopropylsilyl)oxy]phenyl}propanoyl}-*L*-valinate (S37):**

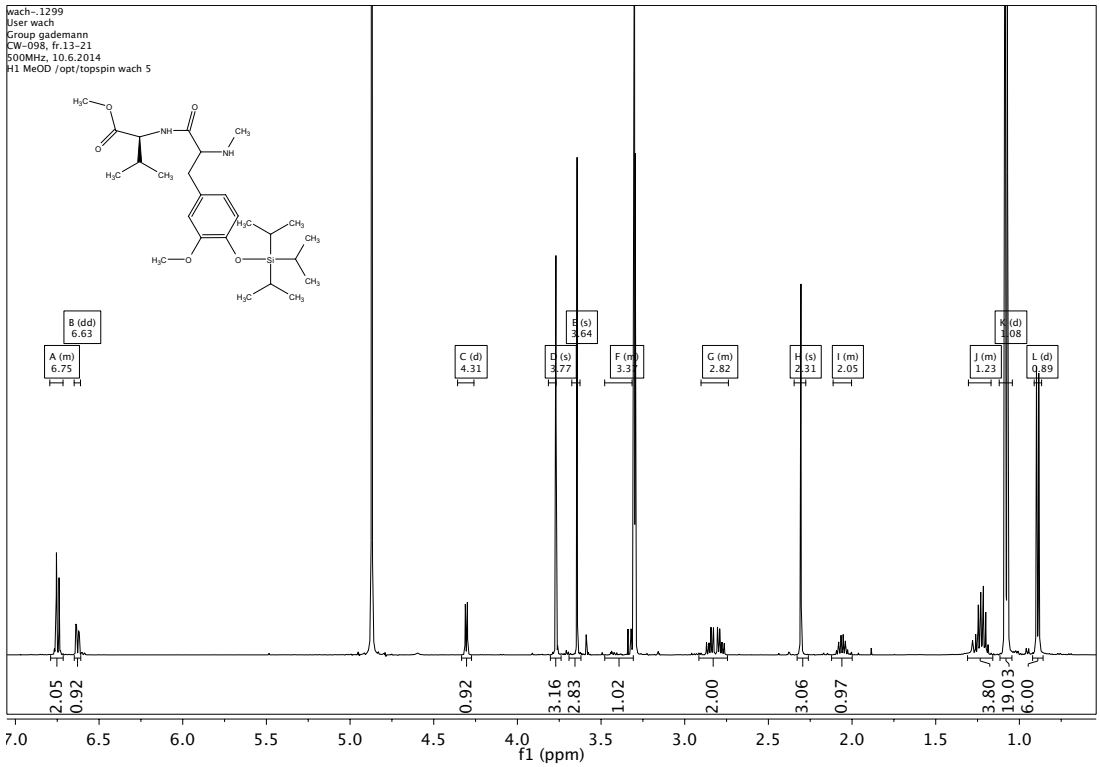


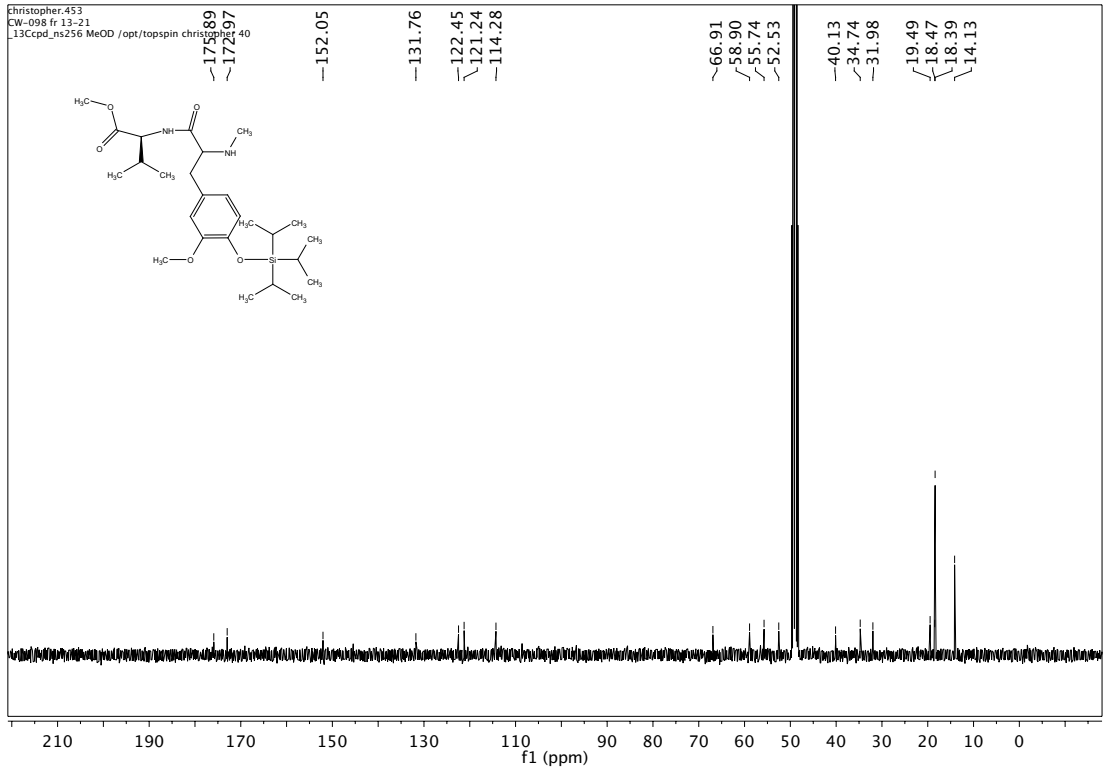




wach-.1289
User wach
Group gademann
CW-097
_HMBC_GPSW MeOD /opt/topspin wach 28
{0.91,57.91}
{1.19,65.51}
{3.74,150.75}
{2.90,157.18}
{4.32,171.99}
{3.71,172.01}
f2 (ppm)
f1 (ppm)

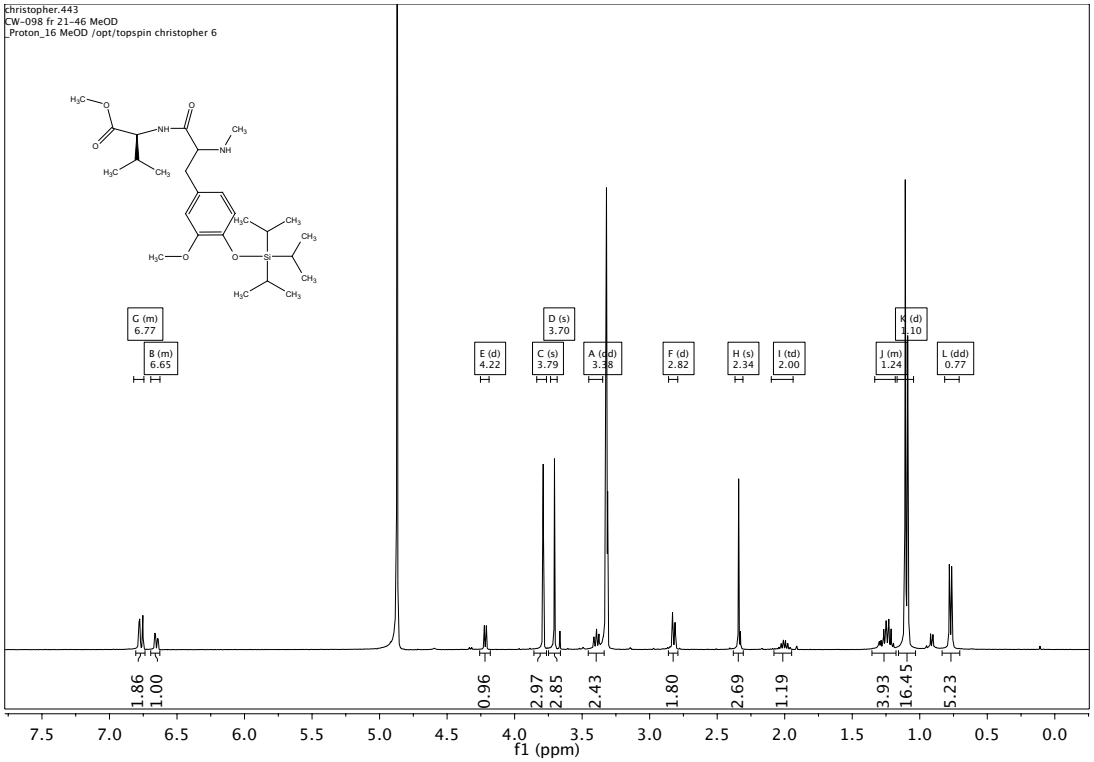
**Methyl {(*R*)-3-(3-methoxy-4-[(triisopropylsilyl)oxy]phenyl}-2-(methylamino)-propanoyl}-*L*-valinate (3.104)**

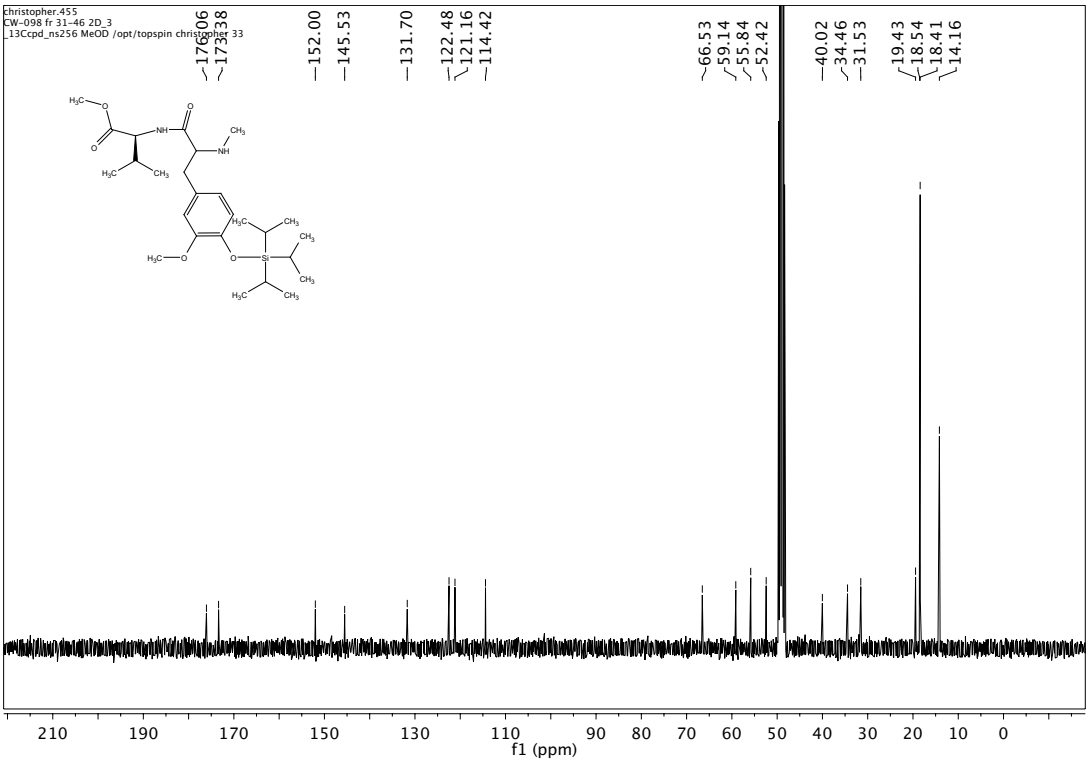
**Minor diastereomer:**



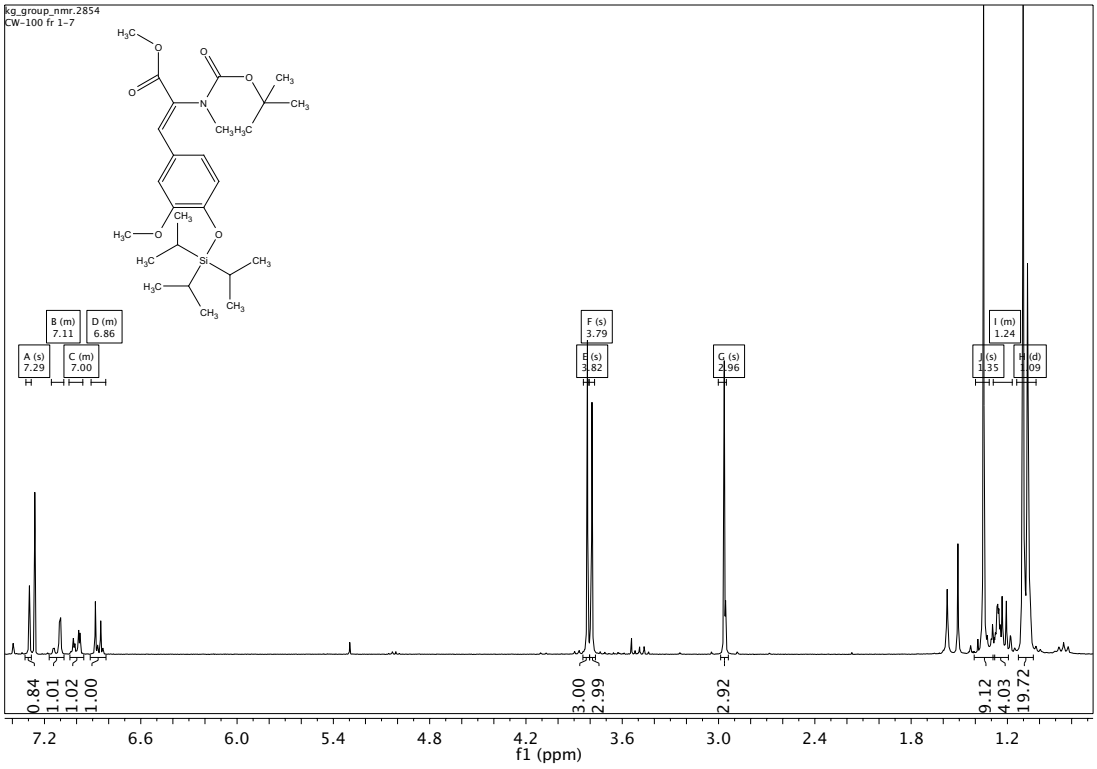



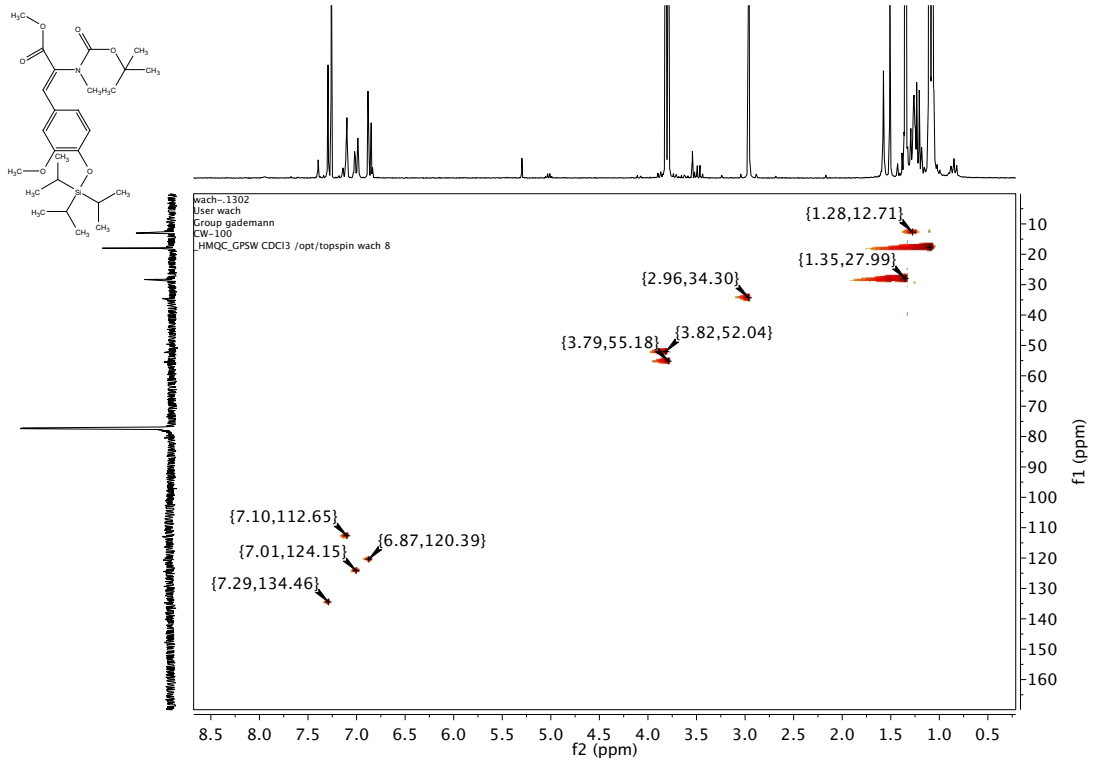
## Major diastereomer (3.103):

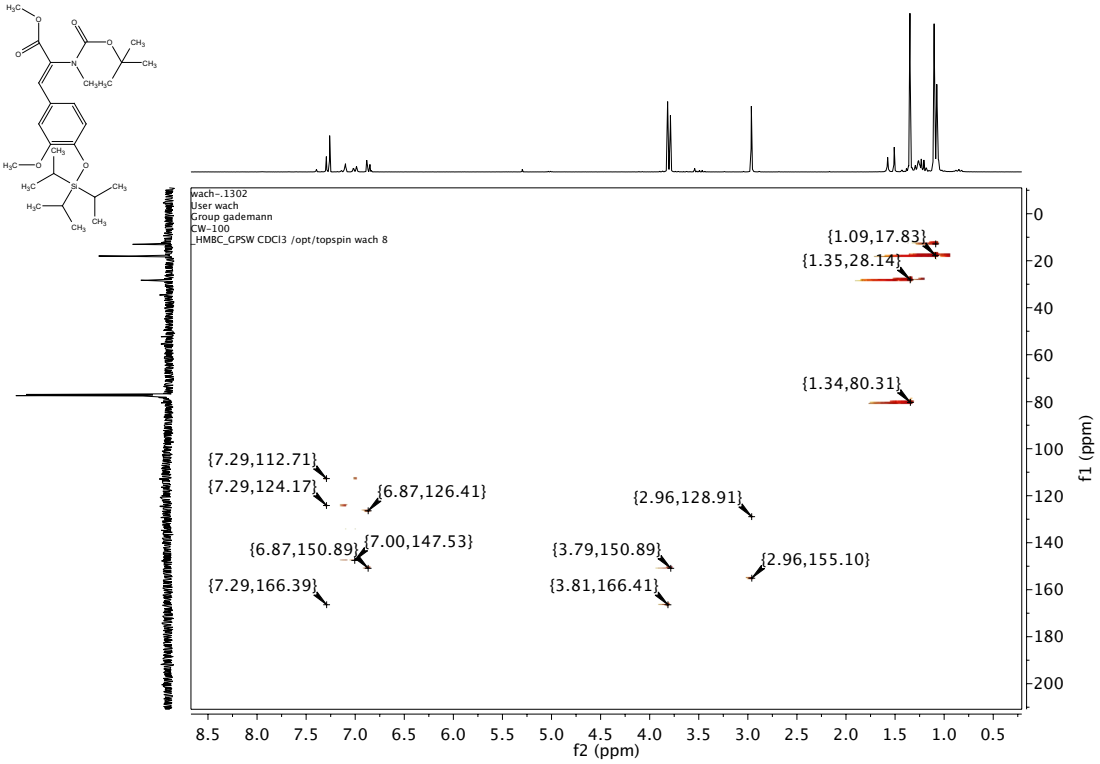


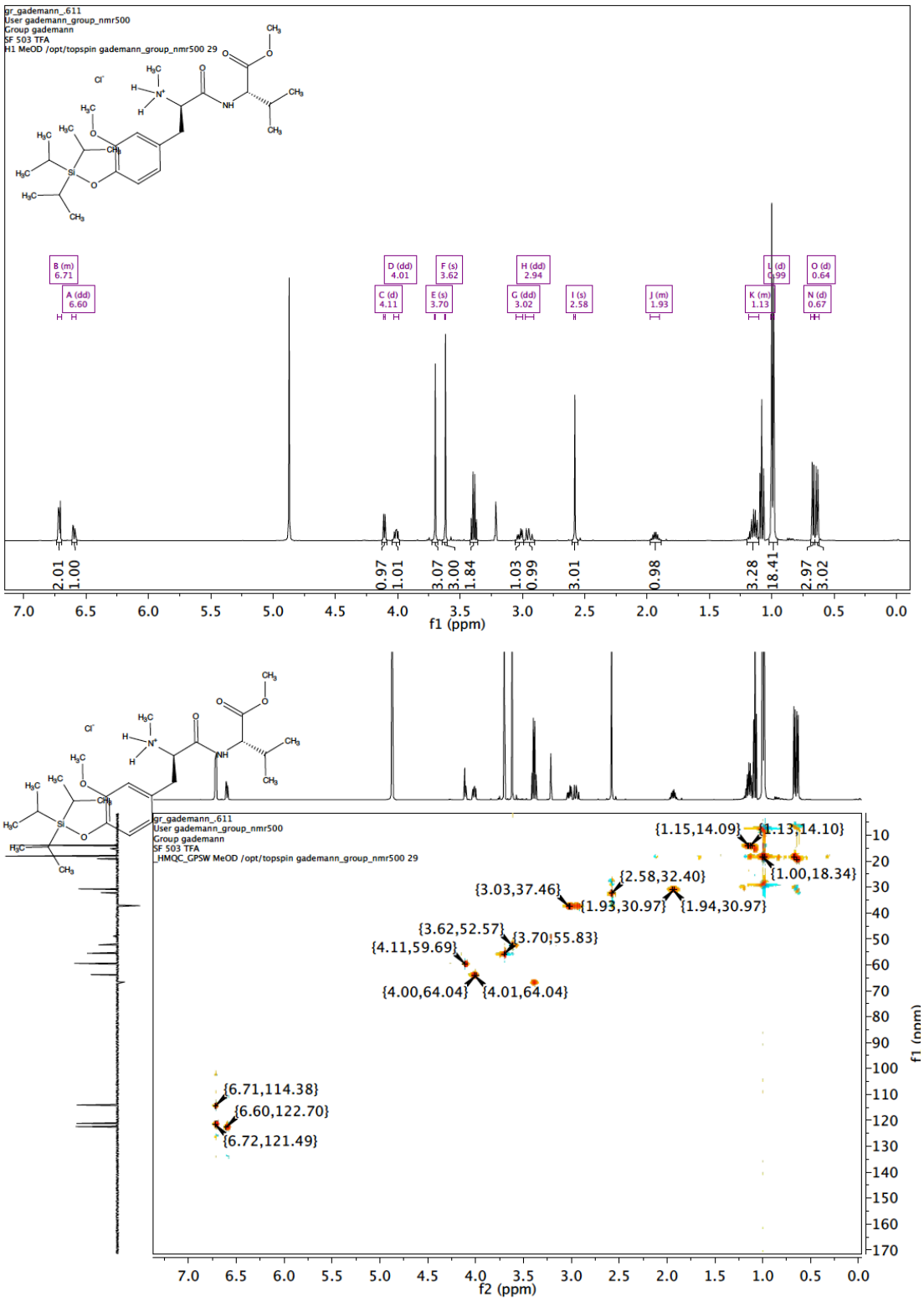
**Methyl (*Z*)-2-[(*tert*-butoxycarbonyl)(methyl)amino]-3-{3-methoxy-4-[(triisopropyl-silyl)oxy]phenyl}acrylate (S38):**

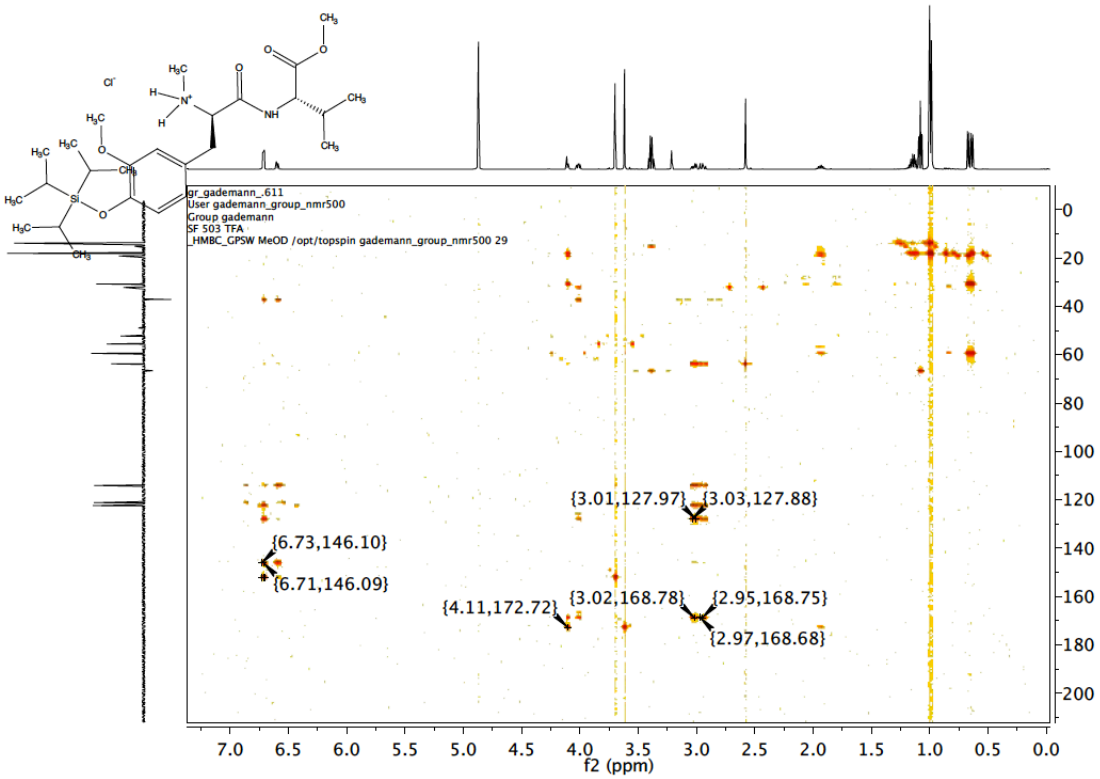


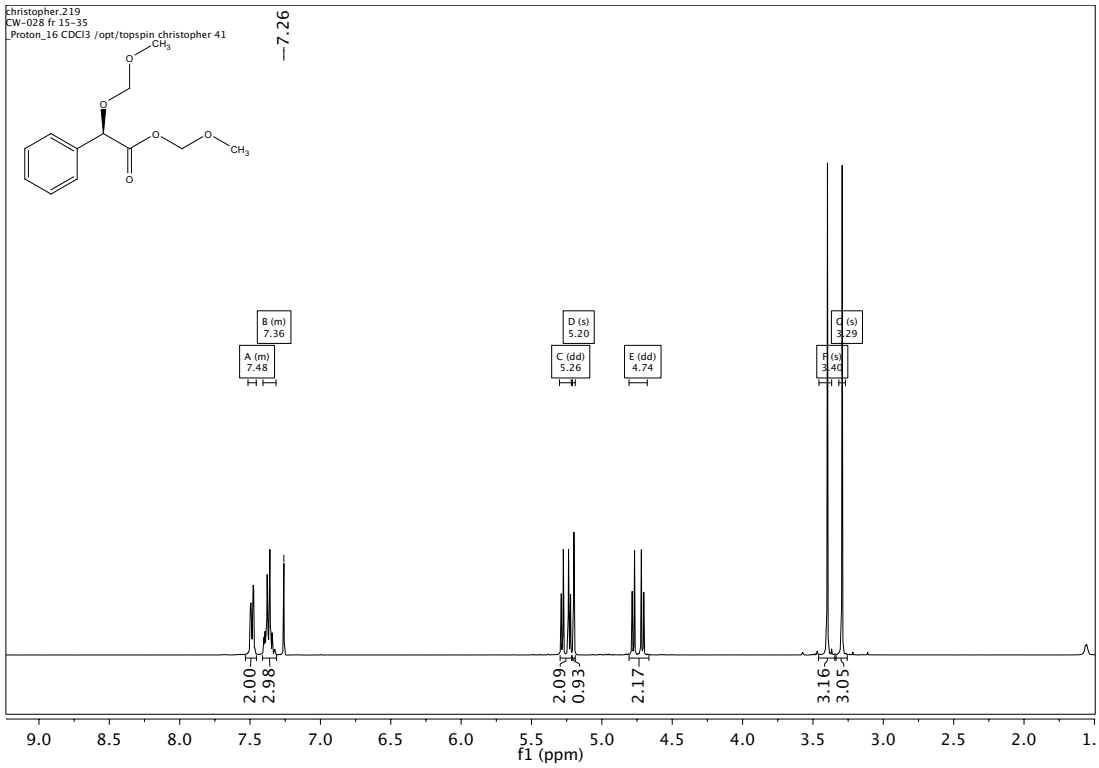

wach~.1302
User wach
Group gademann
CW-100
_HMBC_GPSW CDCl3 /opt/topspin wach 8
{1.09,17.83}
{1.35,28.14}
{1.34,80.31}
{7.29,112.71}
{7.29,124.17}
{6.87,126.41}
{2.96,128.91}
{6.87,150.89}
{7.00,147.53}
{3.79,150.89}
{2.96,155.10}
{7.29,166.39}
{3.81,166.41}
f2 (ppm)
f1 (ppm)

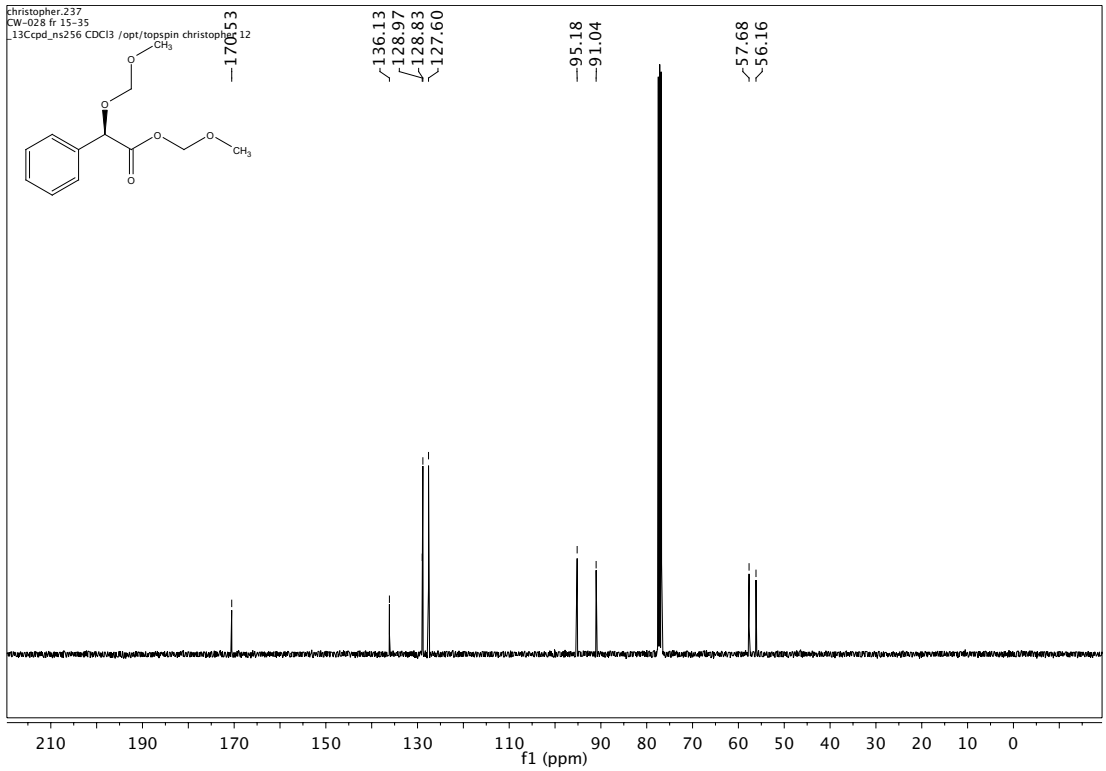
**(*R*)-1-(((*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-*N*-methyl-1-oxopropan-2-aminium chloride (3.112):**



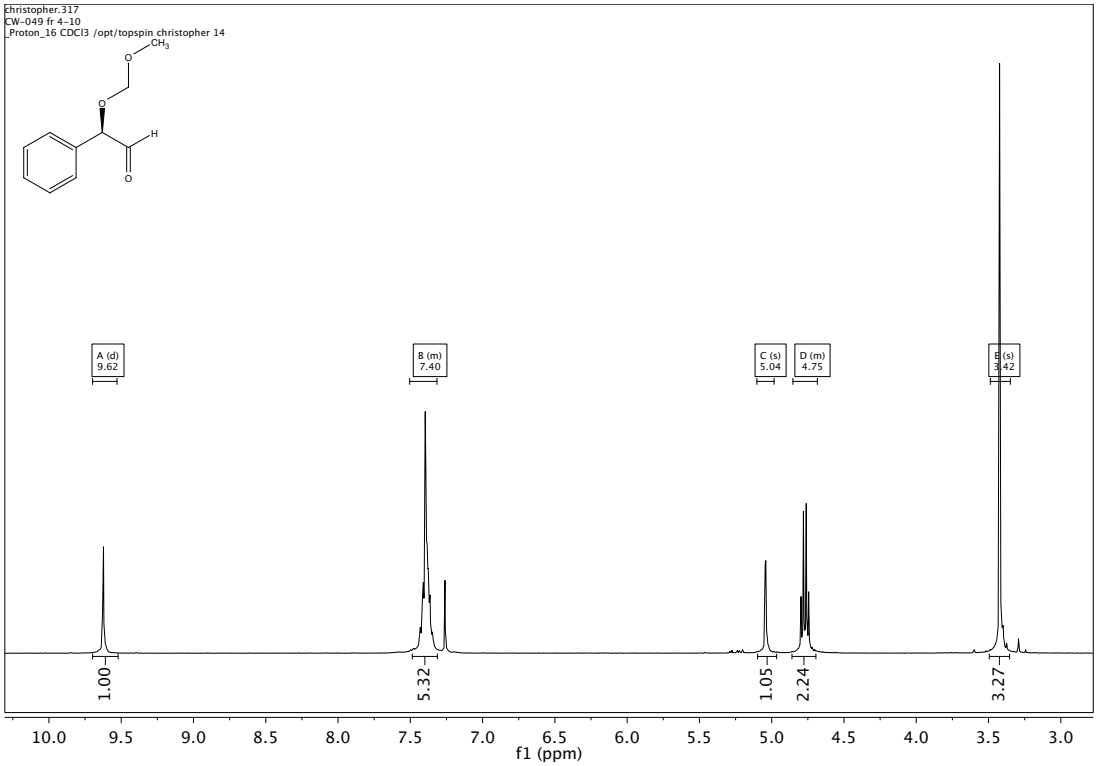

gr_gademann_.611
User gademann_group_nmr500
Group gademann
SF 503 TFA
_HMBC_GPSW MeOD /opt/topspin gademann_group_nmr500 29
{3.01,127.97}
{3.03,127.88}
{6.73,146.10}
{6.71,146.09}
{4.11,172.72}
{3.02,168.78}
{2.95,168.75}
{2.97,168.68}
f2 (ppm)

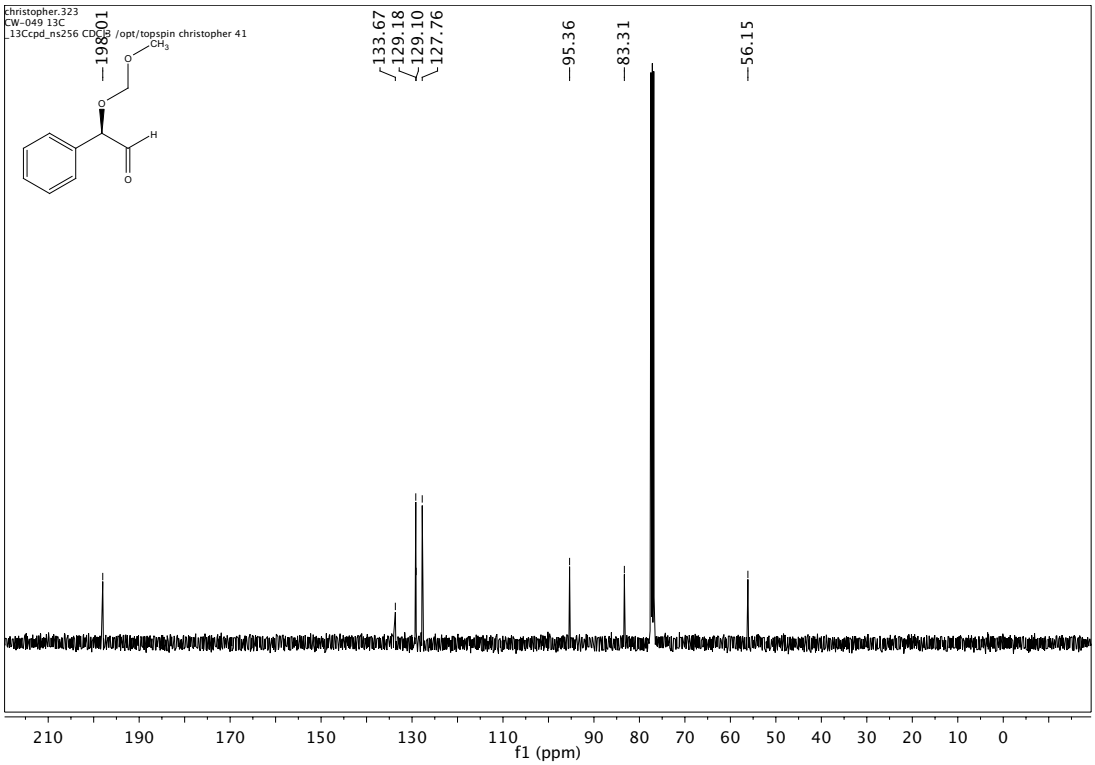
**Methoxymethyl (*R*)-2-(methoxymethoxy)-2-phenylacetate (S39):**



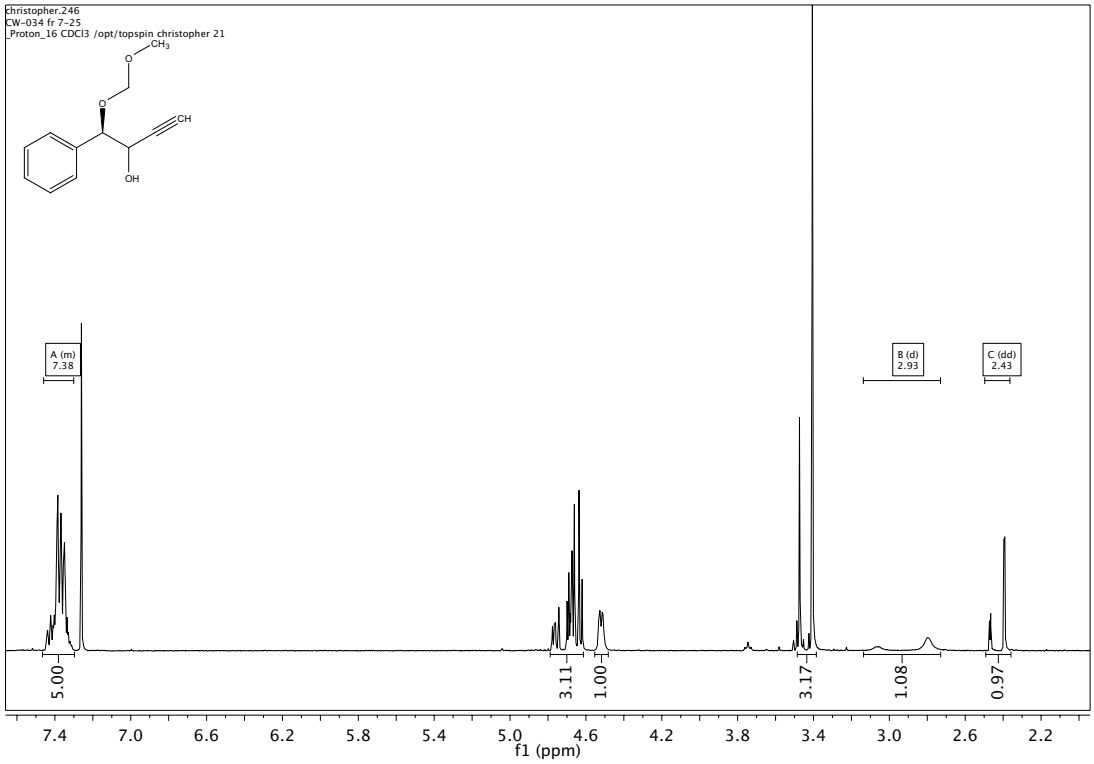



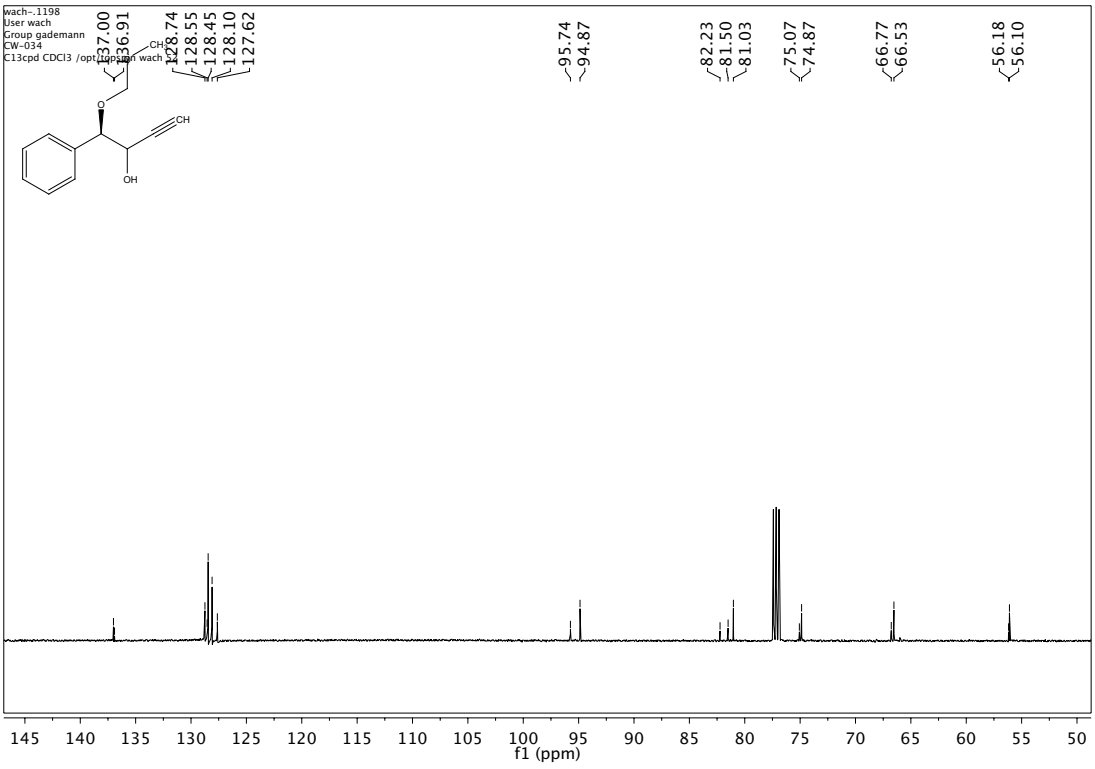
## (*R*)-2-(Methoxymethoxy)-2-phenylacetaldehyde (3.83):



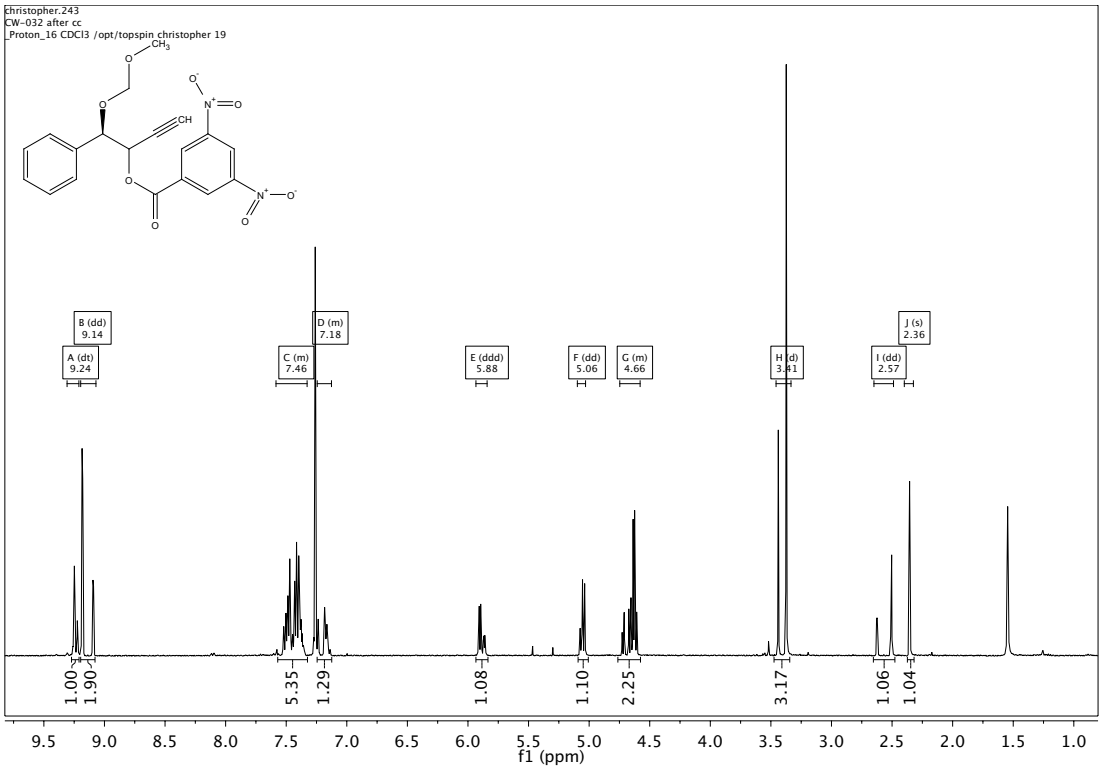



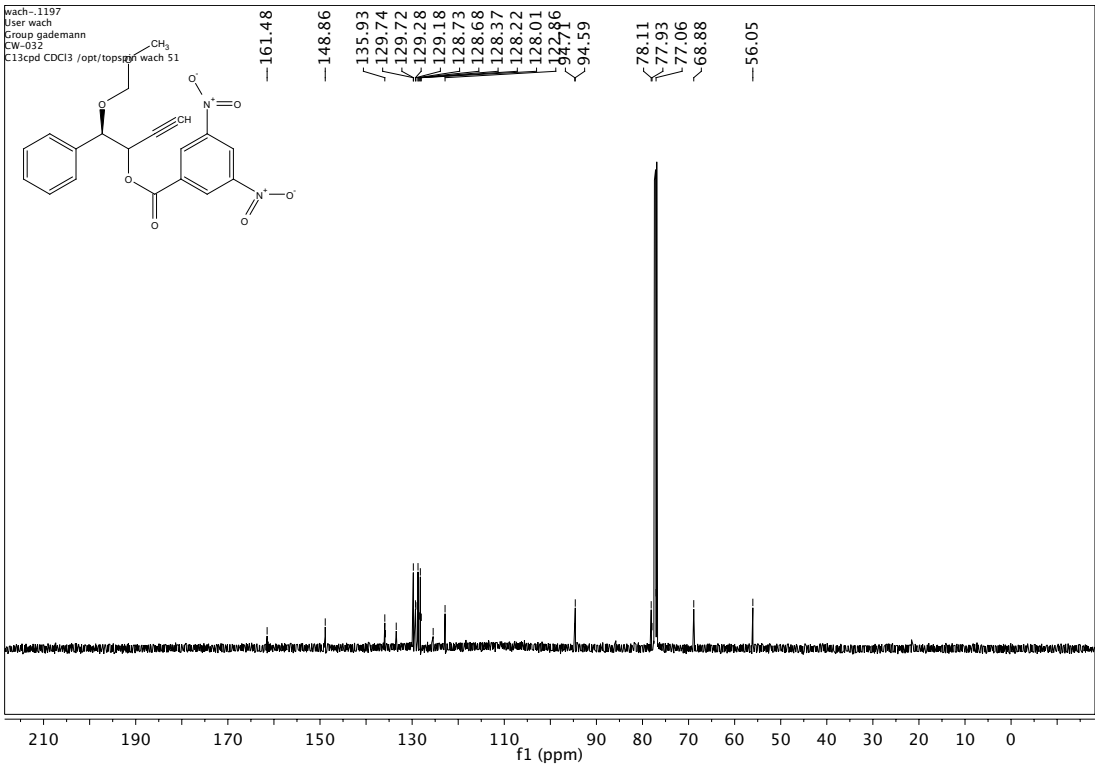
## (1*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-ol (3.84):



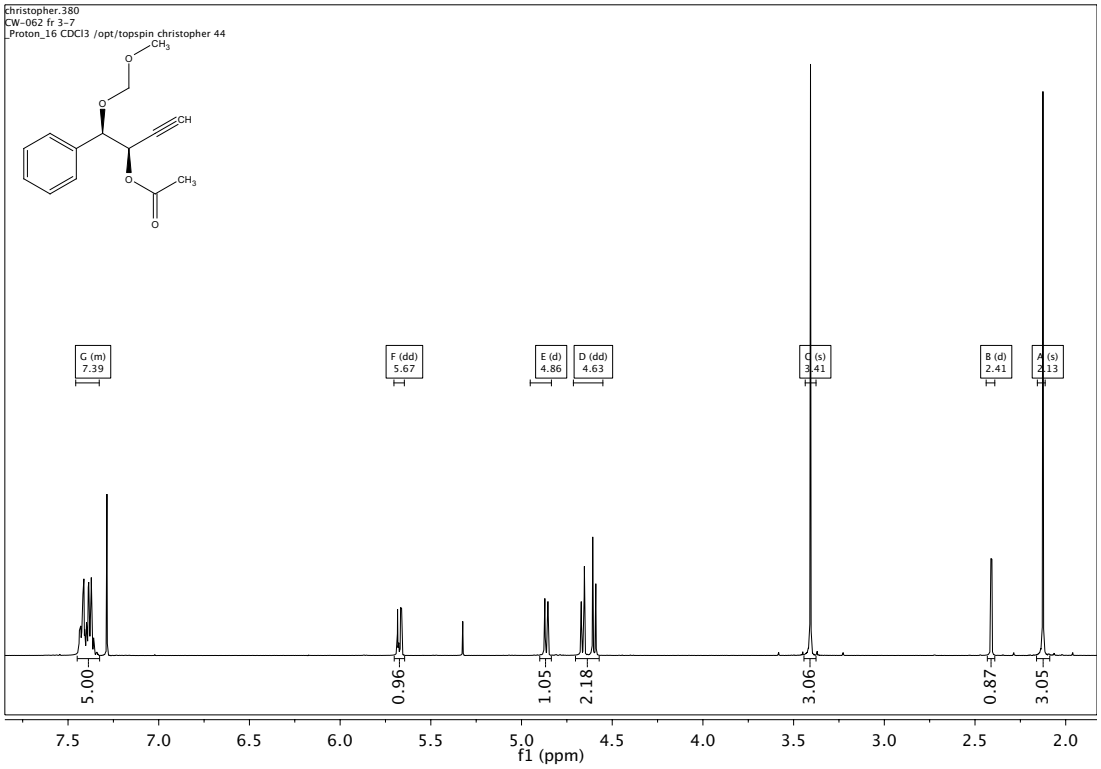



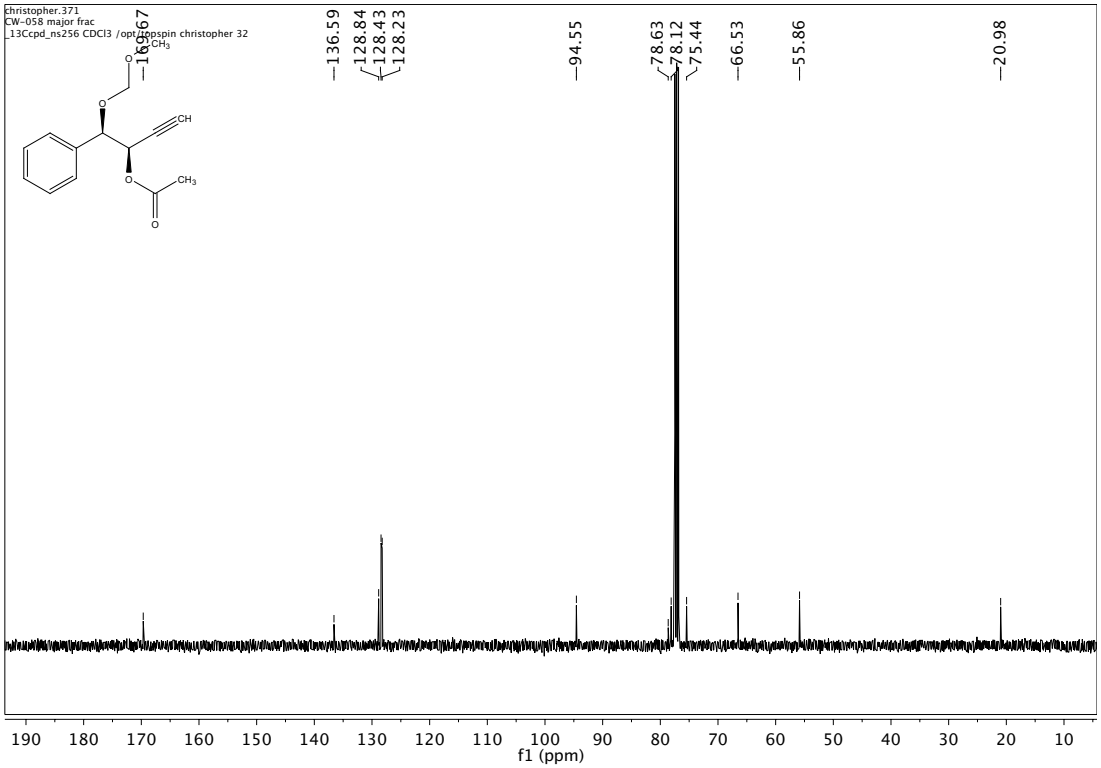
**(1*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-yl 3,5-dinitrobenzoate (S40):**



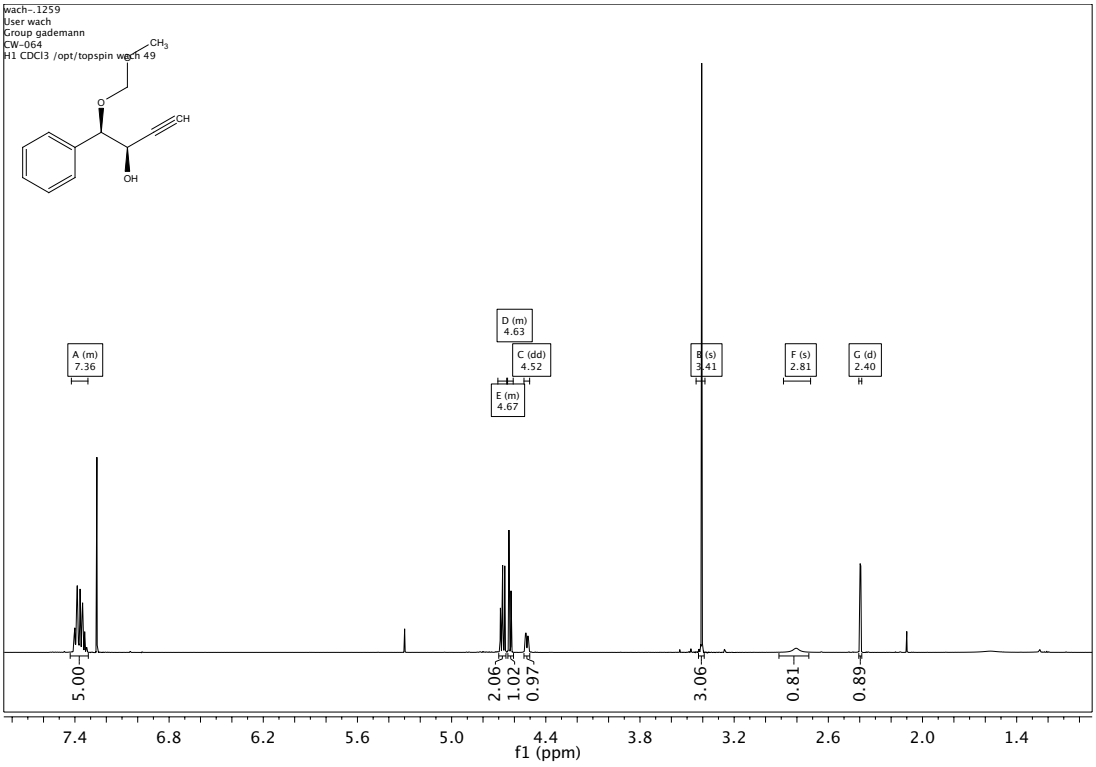



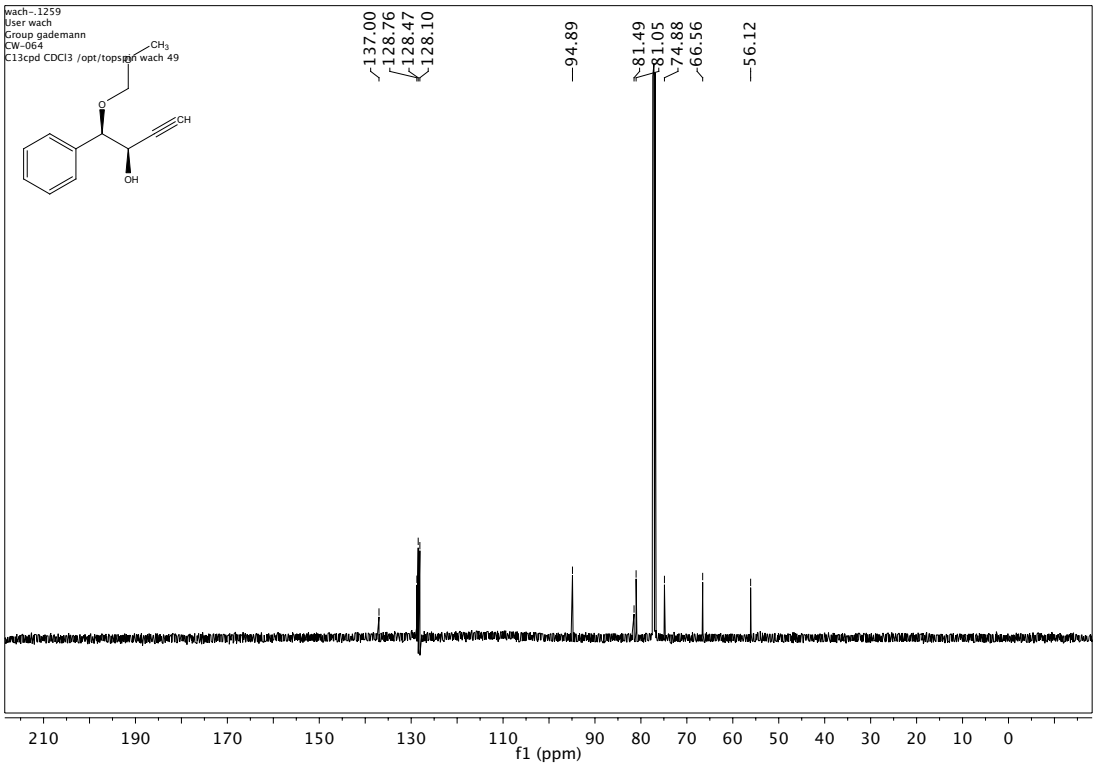
## (1*R*,2*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-yl acetate (3.91):



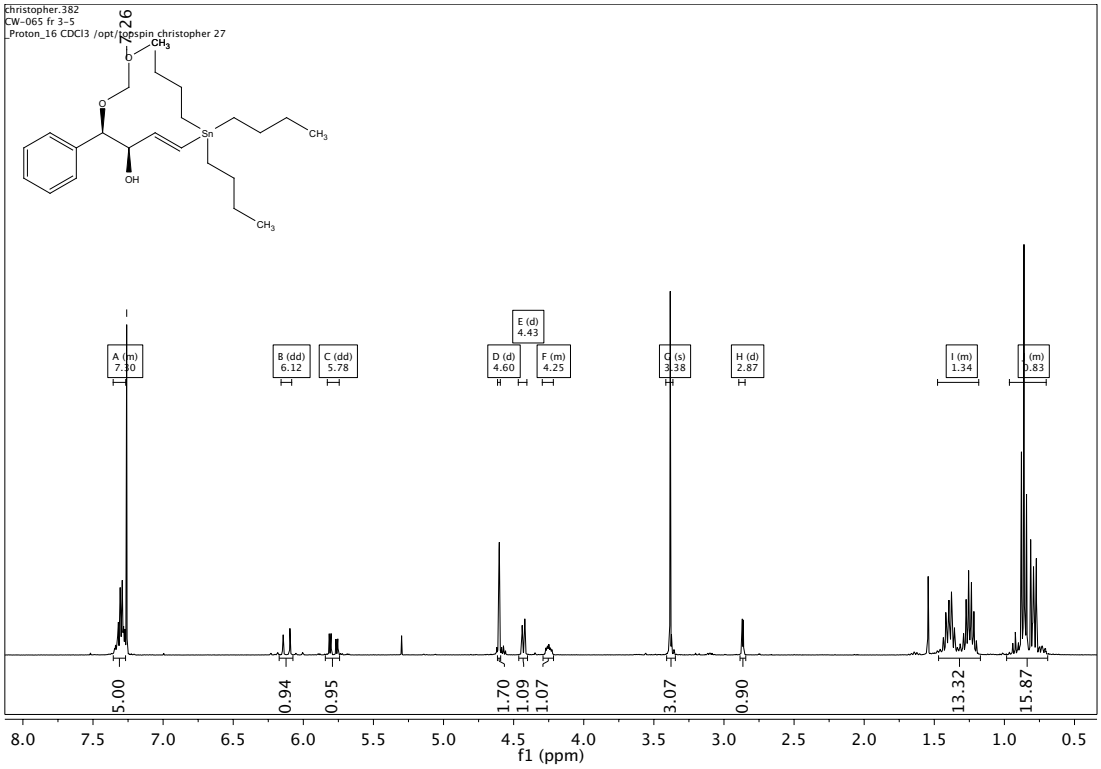



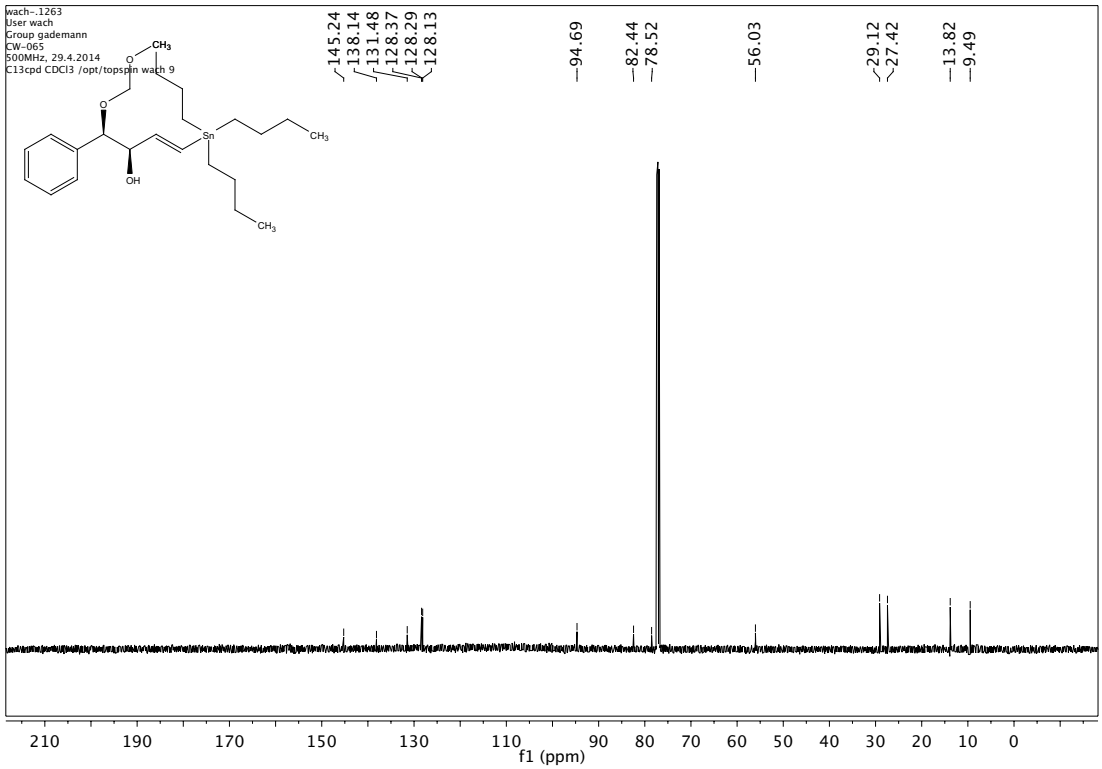
**(1*R*,2*R*)-1-(Methoxymethoxy)-1-phenylbut-3-yn-2-ol (3.92):**



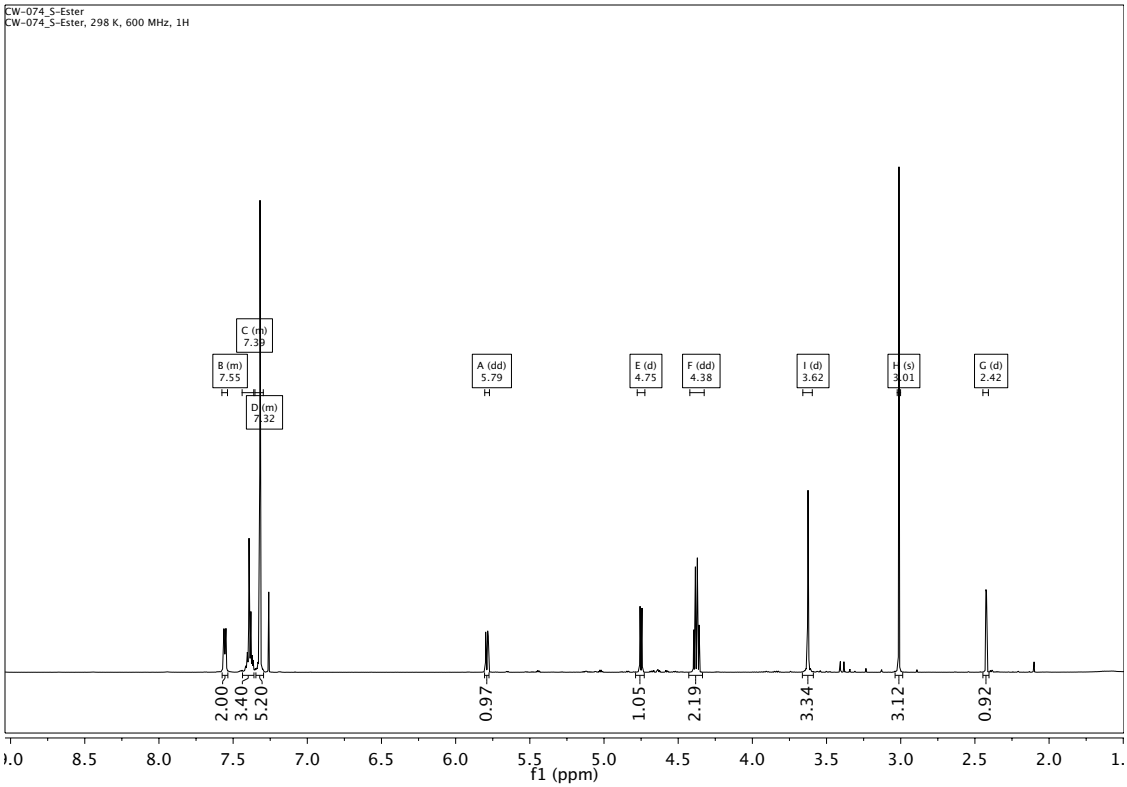



**(1*R*,2*R*,*E*)-1-(Methoxymethoxy)-1-phenyl-4-(tributylstannyl)but-3-en-2-ol (3.27):**

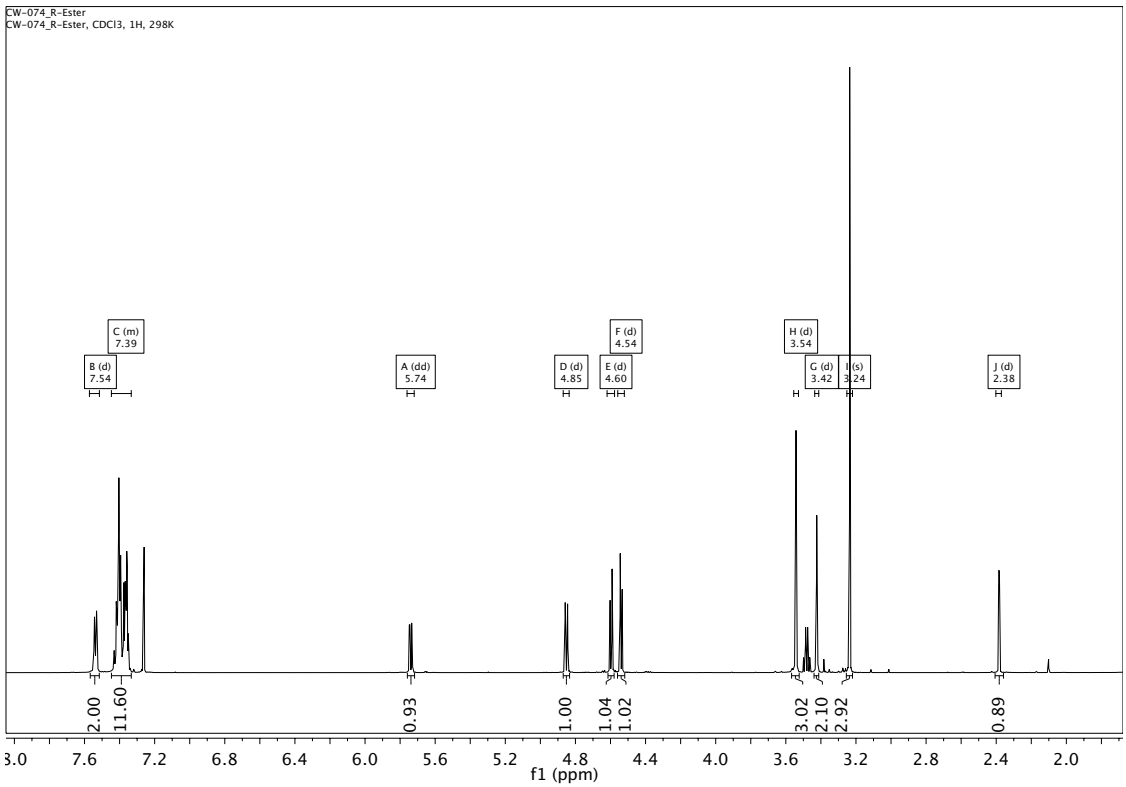


## *S* -MTPA-diol ester (3.93):



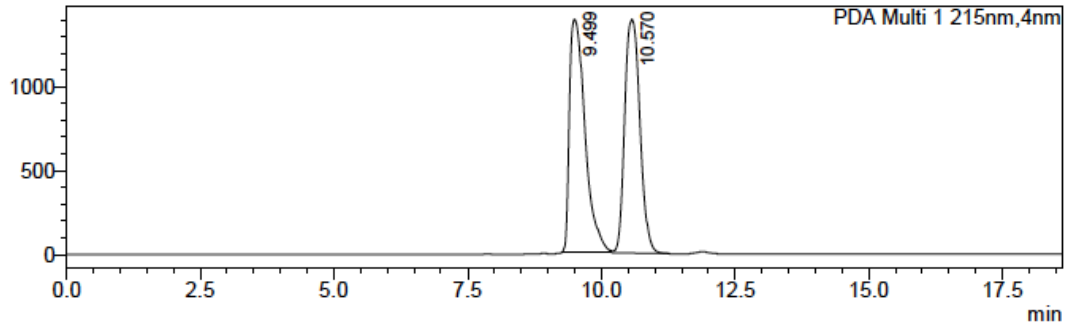

## *R* -MTPA-diol ester (3.94)



# 8 Chiral HPLC Traces

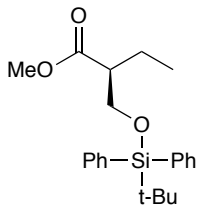
**HPLC Chromatograms**

Racemate chromatogram:

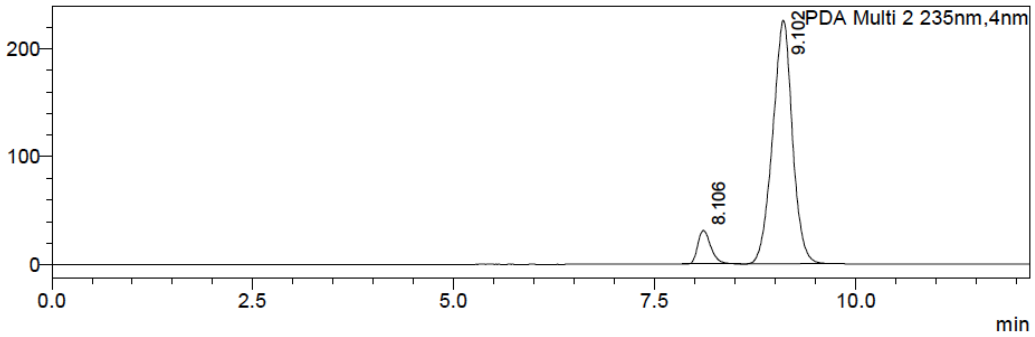



PDA Ch1 215nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 9.499 | 1393221 | 28586796 | 50.820 |
| 2 | 10.570 | 1395152 | 27664142 | 49.180 |
| Total | | 2788373 | 56250938 | 100.000 |




Enantioenriched chromatogram of ester **2.70**:



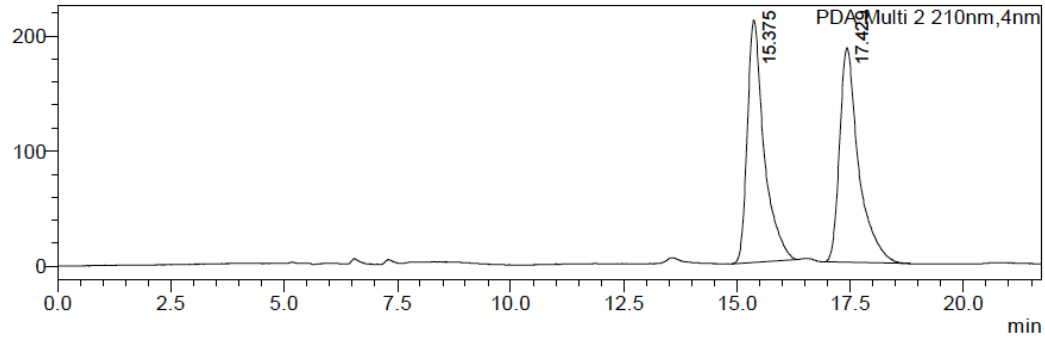

PDA Ch2 235nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 8.106 | 31205 | 354929 | 8.413 |
| 2 | 9.102 | 225767 | 3863820 | 91.587 |
| Total | | 256972 | 4218750 | 100.000 |

OD-H (4.6 mm x 250 mm, Daicel Chemical Industries); 99:1 Heptane/*i*PrOH; 0.5 mL/min; 20 °C

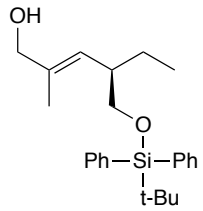
$t_R$= 9.50 min; $t_S$=10.57 min

racemate chromatogram:

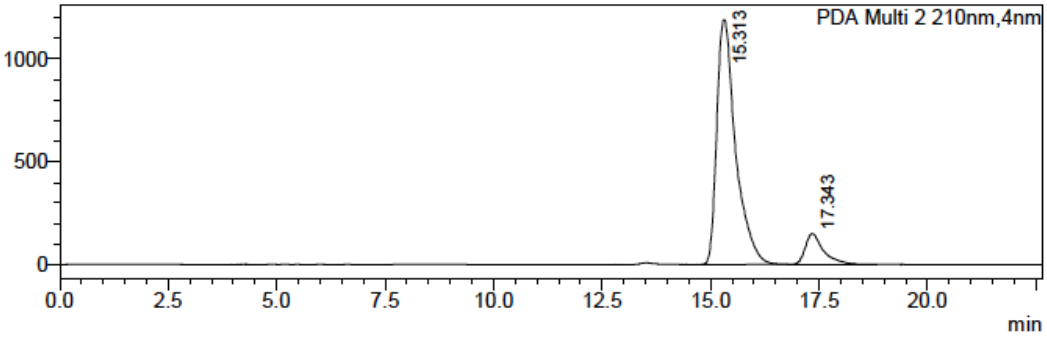



PDA Ch2 210nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 15.375 | 210201 | 5399441 | 49.780 |
| 2 | 17.429 | 186441 | 5447159 | 50.220 |
| Total | | 396642 | 10846599 | 100.000 |




enantioenriched chromatogram of alcohol **S2**:




PDA Ch2 210nm

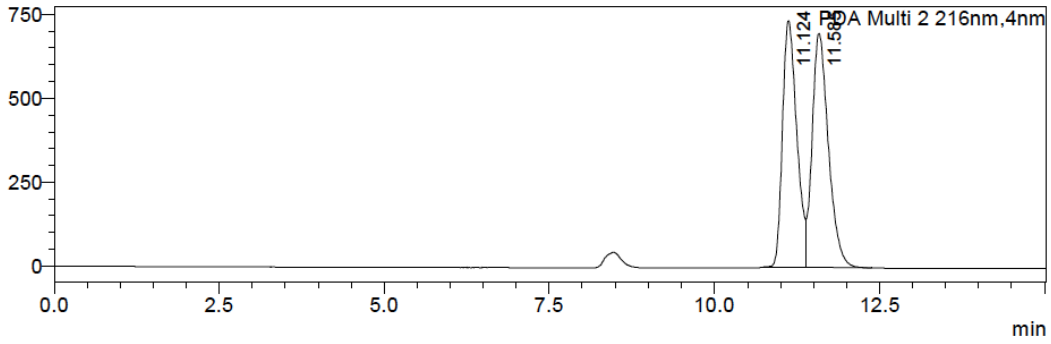
| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 15.313 | 1192341 | 35990614 | 89.150 |
| 2 | 17.343 | 149907 | 4380451 | 10.850 |
| Total | | 1342248 | 40371065 | 100.000 |

AD-H (4.6 mm x 250 mm, Daicel Chemical Industries); 99:1 Heptane/*i*PrOH; 0.6 mL/min; 20 °C

$t_R$= 15.3 min

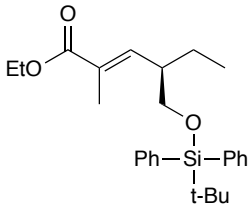
$t_S$= 17.7 min

racemate chromatogram:

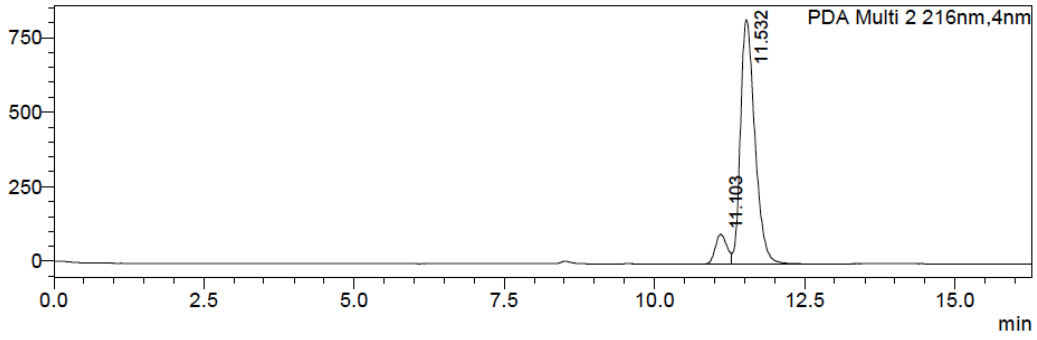



PDA Ch2 216nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 11.124 | 734831 | 11162845 | 48.430 |
| 2 | 11.585 | 697346 | 11886782 | 51.570 |
| Total | | 1432178 | 23049626 | 100.000 |




enantioenriched chromatogram **2.71**:




PDA Ch2 216nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 11.103 | 99017 | 1337878 | 8.931 |
| 2 | 11.532 | 818819 | 13642884 | 91.069 |
| Total | | 917836 | 14980762 | 100.000 |

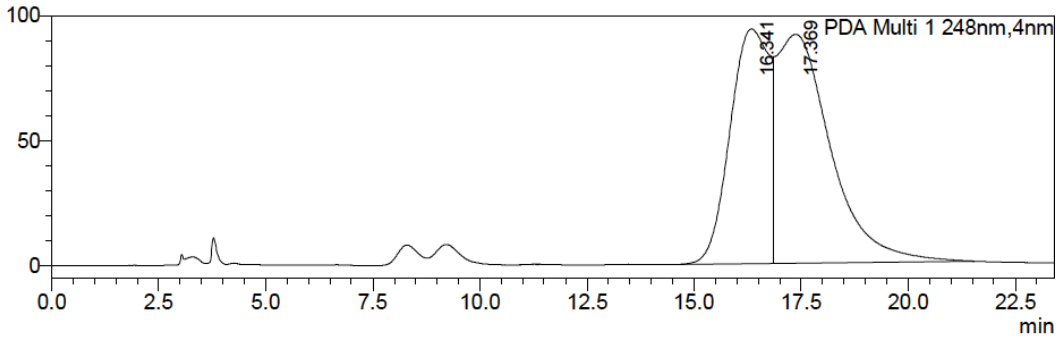
IC (Chiralcel); 99:1 Heptane/*i*PrOH; 0.6 mL/min; 20 °C

$t_S$= 11.1 min

$t_R$= 11.6 min

## Determination of Enantiopurity of (–)-Pyridovericin (2.46)

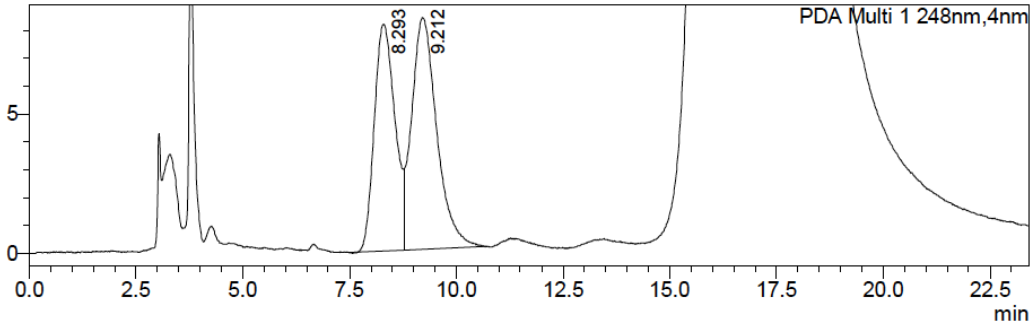
Racemate whole chromatogram:




PDA Ch1 248nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 16.341 | 93810 | 5932887 | 42.458 |
| 2 | 17.369 | 91494 | 8040682 | 57.542 |
| Total | | 185304 | 13973569 | 100.000 |

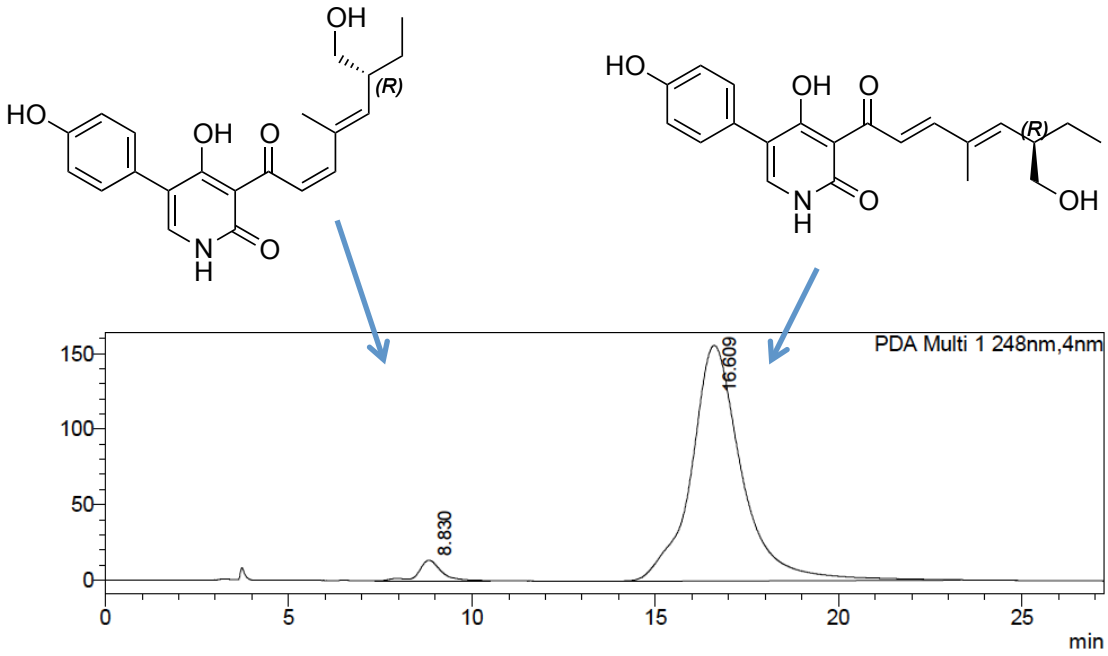
Magnified racemate chromatogram:




PDA Ch1 248nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 8.293 | 8130 | 273480 | 44.484 |
| 2 | 9.212 | 8294 | 341303 | 55.516 |
| Total | | 16423 | 614784 | 100.000 |

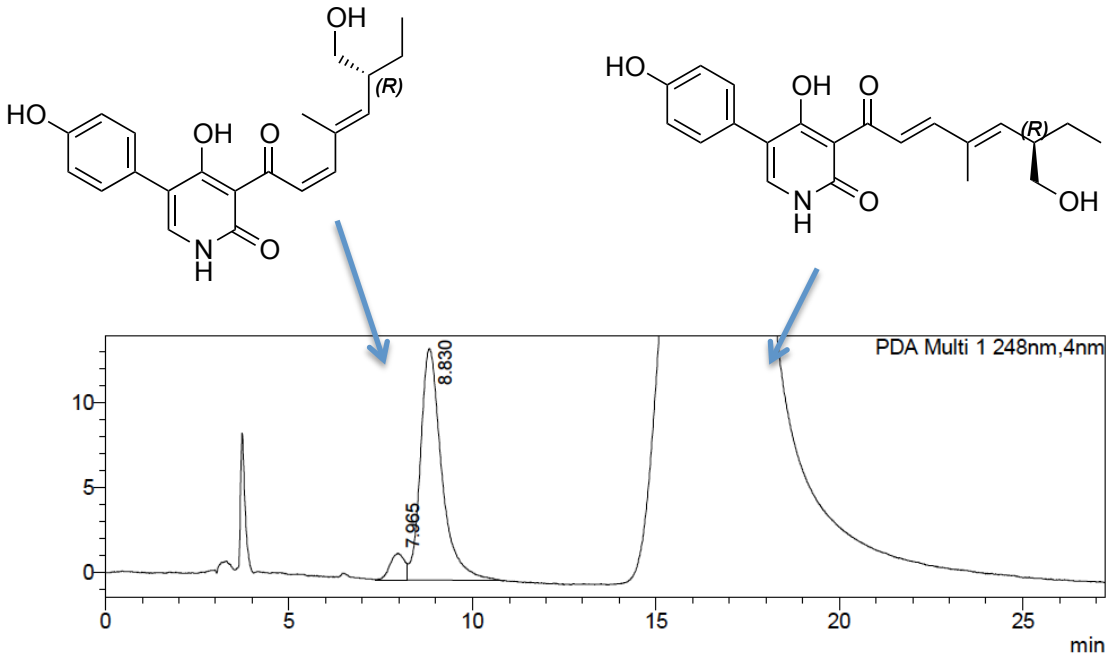
Enantioenriched whole chromatogram:




PDA Ch1 248nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 8.830 | 13563 | 576231 | 3.715 |
| 2 | 16.609 | 155888 | 14935701 | 96.285 |
| Total | | 169451 | 15511932 | 100.000 |

Enantioenriched magnified chromatogram:




PDA Ch1 248nm

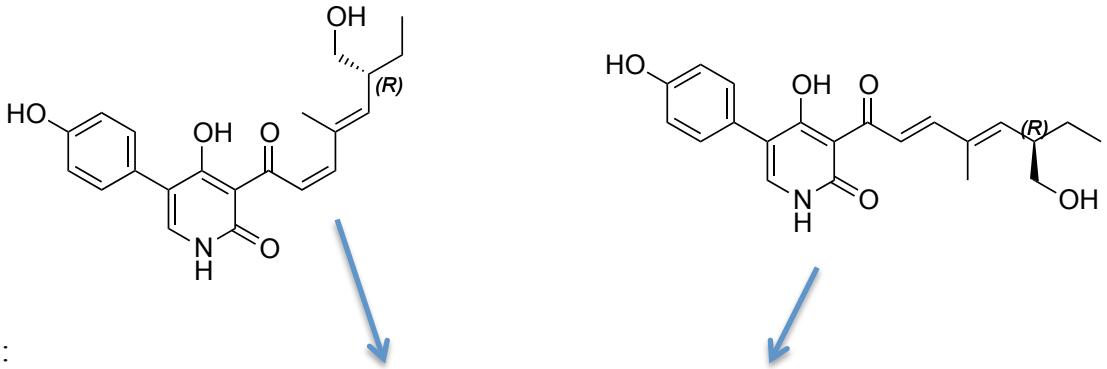
| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 7.965 | 1558 | 43474 | 7.325 |
| 2 | 8.830 | 13644 | 550052 | 92.675 |
| Total | | 15202 | 593527 | 100.000 |

IC (Chiralcel); 70:30 Heptane/*i*PrOH; 1.0 mL/min; 20 °C Retention times for the *Z*-isomer:

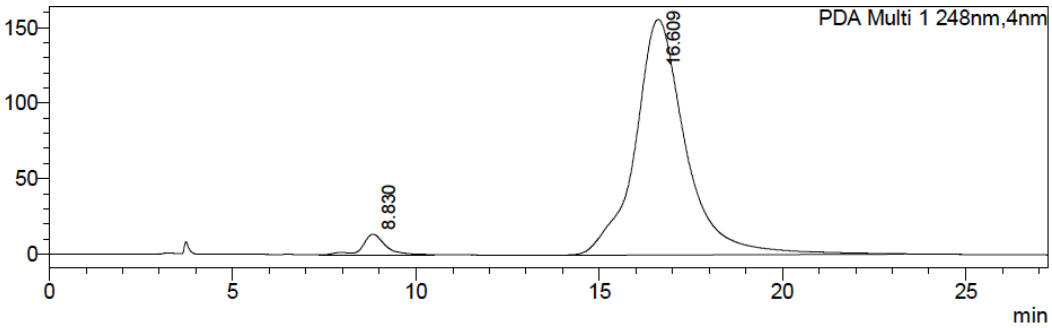
$t_S$ = 8.0 min; $t_R$ = 8.8 min

**_E_/_Z_ Ratio of (–)-Pyridovericin (2.46)**

Enantioenriched chromatogram

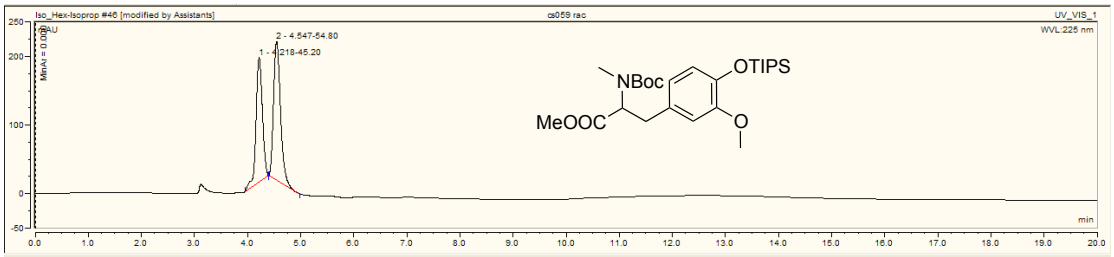



:

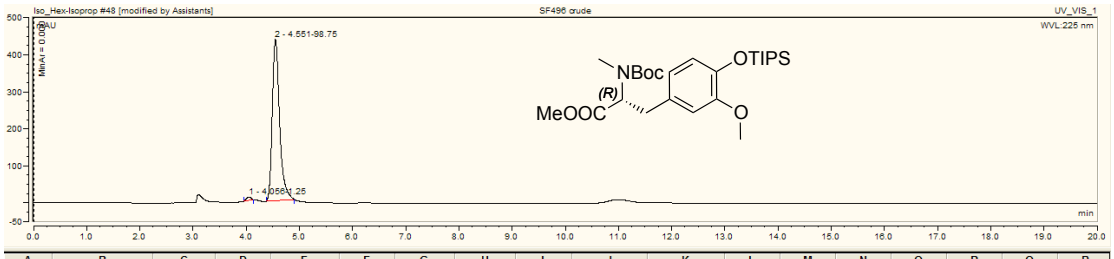



PDA Ch1 248nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 8.830 | 13563 | 576231 | 3.715 |
| 2 | 16.609 | 155888 | 14935701 | 96.285 |
| Total | | 169451 | 15511932 | 100.000 |

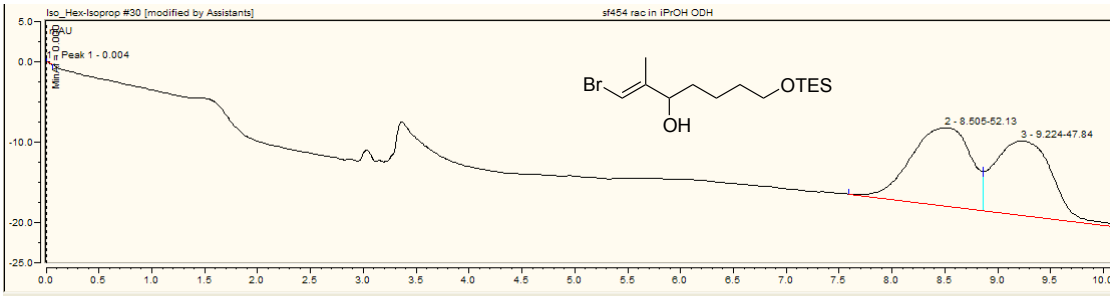



| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | n.a. | 4.218 | 25.2488 | n.a. | BMb* | 181.116 | 45.20 | 1.46 |
| 2 | n.a. | 4.547 | 30.6057 | n.a. | bMB* | 202.285 | 54.80 | n.a. |
| Total: | | | 55.8545 | 0.0000 | | 383.401 | 100.00 | |

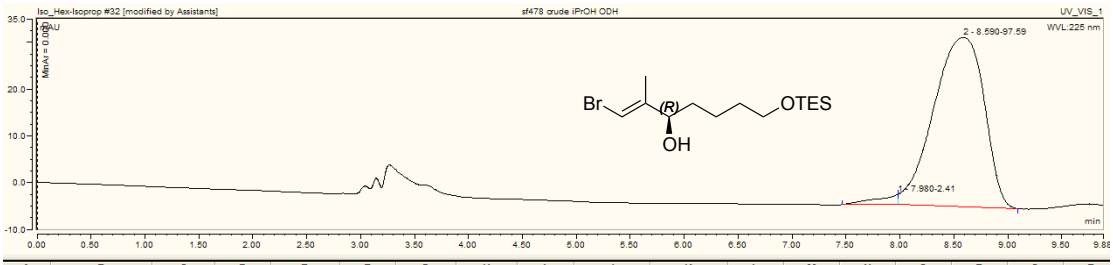



| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | n.a. | 4.056 | 0.8819 | n.a. | BMB* | 8.890 | 1.25 | 2.42 |
| 2 | n.a. | 4.551 | 69.6619 | n.a. | BMB* | 435.370 | 98.75 | n.a. |
| Total: | | | 70.5437 | 0.0000 | | 444.260 | 100.00 | |

Chiral HPLC traces of racemic methylation product **3.105** (up) and enantiopure product **3.111** (below). Chiralpak $I_A$, 95:5 heptane/isopropanol, 1 mL/min, injection vol.: 1 µL, 25 °C, $t_R$ (*S*): 4.12 $t_R$ (*R*): 4.43.



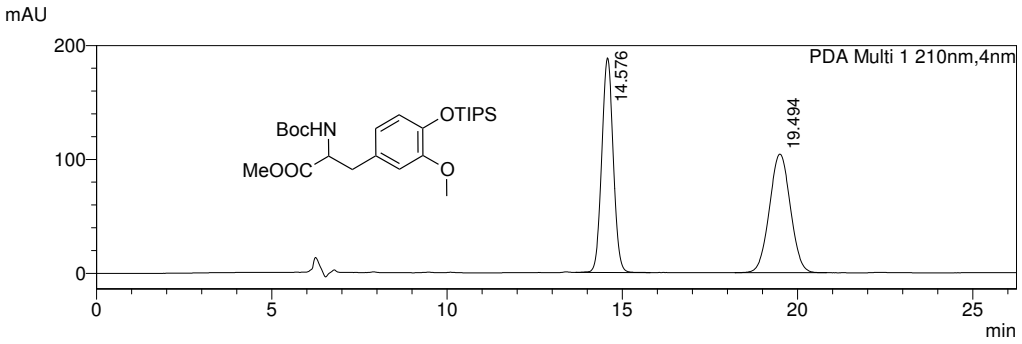

| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | Peak 1 | 0.004 | 0.0036 | n.a. | BMB | 0.031 | 0.03 | n.a. |
| 2 | n.a. | 8.505 | 6.3695 | n.a. | BM | 9.721 | 52.13 | n.a. |
| 3 | n.a. | 9.224 | 5.8444 | n.a. | MB | 9.256 | 47.84 | n.a. |
| Total: | | | 12.2175 | 0.0000 | | 19.008 | 100.00 | |




| No. | Peakname | Ret.Time min | Area mAU*min | Amount | Type | Height mAU | Rel.Area % | Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | n.a. | 7.980 | 0.4854 | n.a. | BM * | 2.159 | 2.41 | n.a. |
| 2 | n.a. | 8.590 | 19.6546 | n.a. | MB* | 36.153 | 97.59 | n.a. |
| Total: | | | 20.1399 | 0.0000 | | 38.312 | 100.00 | |

Chiral HPLC traces of racemic alcohol **S19** (up) and CBS product **S41** (below). Chiralpak OD-H, heptane/isopropanol 99:1, 1.0 mL/min, injection vol.: 1 µL, 25 °C, $t_R$ (*S*): 7.98 min, $t_R$ (*R*): 8.59 min

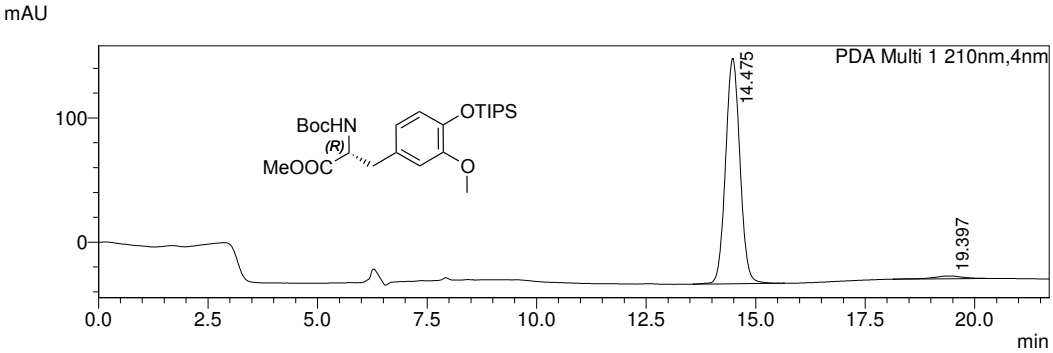
**<Chromatogram>**




PDA Ch1 210nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 14.576 | 188382 | 4277799 | 49.735 |
| 2 | 19.494 | 104166 | 4323462 | 50.265 |
| Total | | 292548 | 8601260 | 100.000 |

**<Chromatogram>**




PDA Ch1 210nm

| Peak# | Ret. Time | Height | Area | Area% |
|---|---|---|---|---|
| 1 | 14.475 | 181438 | 4156489 | 97.668 |
| 2 | 19.397 | 2164 | 99241 | 2.332 |
| Total | | 183603 | 4255730 | 100.000 |

Chiral HPLC trace of racemic amino ester **3.99** (up) and asymmetric hydrogenation product **3.100** (below). Chiralpak $I_A$, 95:5 heptane/isopropanol, 0.5 mL/min, injection vol.: 1 µL, 25°C, $t_R$ (*R*): 14.5 min, $t_R$ (*S*): 19.5 min.).

# 9 CURRICULUM VITAE

Fabian Felix Schmid, born 7th of March 1988 in Basel, Switzerland

10. 2011 – 05.2015 PhD studies in the research group of Prof. Dr. Karl Gademann at the University of Basel : "*Total Synthesis of (–)-Pyridovericin and Synthetic Studies towards Aetheramide B*".

09.2006-03.2011 Bachelor and Master studies at the University of Basel; Master thesis in the research group of Prof. Dr. Karl Gademann : "*Neuritogenic Pyridone Alkaloids: an SAR Study*".

08. 2001 – 06. 2006 Matura, Gymnasium Kirschgarten Basel, Major in Chemistry and Biology.

07. 1994 – 06. 2001 Primar- and Orientierungsschule in Basel

**Teaching Experiences**

During my PhD at the University of Basel, I participated as a teaching assistant in several programs :

- Supervision of undergraduate students (1st-3rd year) in the practical organic chemistry course. Grading reports containing detailed experimental procedures and analytical data.
- Supervision of a master student during his thesis (6 months) and of three BSc students (7 weeks each) in the Gademann group; assisting on planning and conducting experiments and writing reports/master thesis.
- Supervision of a class of 11-13 year old students for one week during the program "Boys at Science" of Schweizer Jugend forscht; assisting experiments demonstrating basic chemical principles.
- Lecture Assistant; preparing, hosting and discussing basic organic chemistry problems for approximately 270 students (Vorlesung OCI).

**List of Publications**

Fabian Schmid, Henning J. Jessen, Maurizio Bernasconi, Andreas Pfaltz and Karl Gademann, **Catalytic Enantioselective Total Synthesis of (–)-Pyridovericin**, *Synthesis* **2014**, *46*, 864.

Patrick Burch, Fabian Schmid, Karl Gademann, **Neuritogenic Surfaces Using Natural Product Analogs**, *Adv. Healthc. Mat.* **2014**, *3*, 1415.

Fabian Schmid, Henning J. Jessen, Patrick Burch and Karl Gademann, **Truncated Militarinone Fragments Identified by Total Chemical Synthesis Induce Neurite Outgrowth**, *Med. Chem. Comm.* **2013**, *49*, 155.

Henning J. Jessen, Andreas Schumacher, Fabian Schmid, Andreas Pfaltz and K. Gademann, **Catalytic Enantioselective Total Synthesis of (+)-Torrubiellone C**, *Org. Lett.* **2011**, *13*, 4368.

**Poster Presentations**

09. 2014 "Synthetic Studies towards Aetheramide B", Fabian Schmid, Christopher Wittwer, Karl Gademann, Regio Symposium, Sornetan, Switzerland.

05. 2014 "Truncated Militarinone Fragments in a Neuritogenic Surface Material" Fabian Schmid, Henning J. Jessen, Patrick Burch and Karl Gademann, Prof. Schönbein memorial symposium, Basel, Switzerland.

09. 2012 "Truncated Militarinone Fragments Identified by Total Chemical Synthesis Induce Neurite Outgrowth" Fabian Schmid, Henning J. Jessen, Patrick Burch and Karl Gademann, SCS Fall meeting, ETH Zürich, Switzerland

**Languages**

German (mother tongue), English (fluent), French (good knowledge).